TOXICOLOGICAL PROFILE FOR SULFUR DIOXIDE

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

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
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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 the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous 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 hazardous 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.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff 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.

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare 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. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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: Health Effects: Specific health effects of a given hazardous compound are reported by route *of exposure,* by *type of health effect* (death, systemic, immunologic, reproductive), 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:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: l-800-447-1544 (to be replaced by l-888-42-ATSDR in 1999)
or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@,cdc.gov ***Internet:*** http://atsdrl.atsdr.cdc.gov:8080

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History-The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

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 l •Phone: 770-488-7000 l 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, 200 Independence Avenue, SW, Washington, DC 20201 •Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19,4676 Columbia Parkway, Cincinnati, OH 45226-1998 •Phone: 800-35-NIOSH.

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.

Referrals

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, #5 13, Washington, DC 20005 •Phone: 202-347-4976 •FAX: 202-347-4950 •e-mail: aoec@,dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

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, 55 West Seegers Road, Arlington Heights, IL 60005 •Phone: 847-228-6850 •FAX: 847-228-1856.

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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 . Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for Sulfur dioxide. The panel consisted of the following members:

1. Edward Avol, Associate Professor, Department of Preventive Medicine, School of Medicine, University of Southern California, Los Angeles, CA

2 . Ingeborg Harding-Barlow, Ph.D., Private Consultant, Palo Alto, CA

3 . Clint Skinner, Ph.D., Skinner Associates, Creston, CA.

These experts collectively have knowledge of sulfur dioxide'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(1)(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. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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

This public health statement tells you about sulfur dioxide and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Sulfur dioxide has been found in at least 16 of the 1,467 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which sulfur dioxide is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance 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. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to sulfur dioxide, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1 .1 WHAT IS SULFUR DIOXIDE?

Sulfur dioxide is a colorless gas with a pungent odor. It is a liquid when under pressure. Sulfur dioxide dissolves in water very easily. It cannot catch fire.

Sulfur dioxide in the air results primarily from activities associated with the burning of fossil fuels (coal, oil) such as at power plants or from copper smelting. In nature, sulfur dioxide can be

released to the air, for example, from volcanic eruptions. Chapters 3 and 4 contain further information.

1.2 WHAT HAPPENS TO SULFUR DIOXIDE WHEN IT ENTERS THE ENVIRONMENT?

Once released into the environment, sulfur dioxide moves to the air. In the air, sulfur dioxide can be converted to sulfuric acid, sulfur trioxide, and sulfates. Sulfur dioxide dissolves in water. Once dissolved in water, sulfur dioxide can form sulfurous acid. Soil can absorb sulfur dioxide, but we do not know if or how it moves in soil. Chapters 4 and 5 contain further information.

1.3 HOW MIGHT I BE EXPOSED TO SULFUR DIOXIDE?

You may be exposed to sulfur dioxide mainly by breathing air that contains it. You may also be exposed to sulfur dioxide by skin contact with it.

The people most often exposed to sulfur dioxide are workers in plants where sulfur dioxide occurs as a by-product, such as in the copper smelting industry and in the processing or burning of coal or oil. Other exposures occur in the manufacture of sulfuric acid, paper, food preservatives, and fertilizers. The primary way that workers are exposed to sulfur dioxide is through the air. Workers may be exposed to concentrations of sulfur dioxide that are higher than typical outdoor air levels. People living near heavily industrial activities that involve smelting copper or the processing or burning of coal or oil are also likely to be exposed to sulfur dioxide by breathing it. Chapter 5 contains further information.

1.4 HOW CAN SULFUR DIOXIDE ENTER AND LEAVE MY BODY?

If you breathe air containing sulfur dioxide, you may absorb it into your body through your nose and lungs. Sulfur dioxide can easily and rapidly enter your bloodstream through your lungs. Once in the body, it breaks down to sulfate and leaves through the urine. Chapter 2 contains further information.

1.5 HOW CAN SULFUR DIOXIDE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Short-term exposures to high levels of sulfur dioxide can be life-threatening. Exposure to 100 parts of sulfur dioxide per million parts of air (ppm) is considered immediately dangerous to life and health. Previously healthy nonsmoking miners who breathed sulfur dioxide released as a result of an explosion in an underground copper mine developed burning of the nose and throat, breathing difficulties, and severe airway obstructions. Long-term exposure to persistent levels of sulfur dioxide can also affect your health. Lung function changes have been observed in some workers exposed to 0.4-3.0 ppm sulfur dioxide for 20 years or more. However, these workers were also exposed to other chemicals, making it difficult to attribute their health effects to sulfur dioxide exposure alone. Additionally, exercising asthmatics are sensitive to the respiratory effects of low concentrations (0.25 ppm) of sulfur dioxide.

For comparative purposes, typical outdoor concentrations of sulfur dioxide may range from 0 to 1 ppm. Occupational exposures to sulfur dioxide may lawfully range from 0 to 5 ppm as enforced by your state OSHA (Occupational Safety and Health Administration). During any 8-hour workshift of a 40-hour workweek, the average concentration of sulfur dioxide in the workplace

may not exceed 5 ppm. However, during system malfunctions or unforseen events, levels approaching 50 ppm or more have been reported.

Studies in animals support the human data regarding respiratory effects of sulfur dioxide. At low levels (less than 1 ppm) of sulfur dioxide exposure, guinea pigs displayed changes in their ability to breathe as deeply or as much air per breath. More severe symptoms seen in animals exposed to high concentrations of sulfur dioxide include decreased respiration, inflammation or infection of the airways, and destruction of areas of the lung.

For more information refer to Chapter 2.

1.6 HOW CAN SULFUR DIOXIDE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Since sulfur dioxide is primarily present as a gas, the general public is exposed to it mostly by breathing contaminated air. Levels of sulfur dioxide in the atmosphere vary from region to region and are mainly influenced by the intensity of industry and development usually associated with cities. Therefore, children with the highest exposure to sulfur dioxide are those living near industrial sources (i.e., industries that process or burn coal or oil, copper smelting plants, sulfuric acid manufacturers, fertilizer factories, or paper pulp factories).

Members of the general public may also have additional risk for exposure if they live near a hazardous waste site contaminated with sulfur dioxide. At 16 of the 1,467 NPL hazardous waste sites, sulfur dioxide has been identified in air, surface water, groundwater, soil, or sediment. Children, as well as adults, living near these sites are most likely to be exposed by breathing contaminated air.

Most of the effects of sulfur dioxide exposure that occur in adults (i.e., difficulty breathing, changes in the ability to breathe as deeply or take in as much air per breath, and burning of the nose and throat) are also of potential concern in children, but it is unknown whether children are more vulnerable to exposure. Children may be exposed to more sulfur dioxide than adults because they breathe more air for their body weight than adults do. Children also exercise more frequently than adults. Exercise increases breathing rate. This increase results in both a greater amount of sulfur dioxide in the lungs and enhanced effects on the lungs. One study suggested that a person's respiratory health, and not his or her age, determines vulnerability to the effects of breathing sulfur dioxide. This study implies that healthy adolescents (ages 12-17) are no more vulnerable to the effects of breathing sulfur dioxide than healthy senior citizens.

Long-term studies surveying large numbers of children have indicated possible associations between sulfur dioxide pollution and respiratory symptoms or reduced breathing ability. Children who have breathed sulfur dioxide pollution may develop more breathing problems as they get older, may make more emergency room visits for treatment of wheezing fits, and may get more respiratory illnesses than is typical for children. However, studies like these are unable to provide conclusive evidence about sulfur dioxide's effects on children's health because many other pollutants are also present in the air.

It is known that exercising asthmatics are sensitive to low concentrations of sulfur dioxide. Therefore, increased susceptibility is expected in children with asthma, but it is not known whether asthmatic children are more sensitive than asthmatic adults. Additionally, asthma occurs most often in African Americans, children between the ages of 8 and 11, and people living in cities. For unknown reasons, the death rates associated with asthma are also higher in non-Caucasian people. Therefore, it is expected that asthmatic, African American children living in urban areas have increased sensitivity to sulfur dioxide.

There are few studies which provide evidence of reproductive or developmental effects of sulfur dioxide exposure in humans. One study found no relationship between spontaneous abortion and exposure to sulfur dioxide among women living in an industrial community in Finland. However,

another study in China showed a relationship between decreased infant birth weight and exposure to sulfur dioxide pollution during pregnancy. Another study, in the Czech Republic, showed that 18- year-old males who were exposed to high levels of sulfur dioxide had sperm with more abnormalities and reduced abilities to move. Studies like these, though, are often hard to interpret. It can be difficult to distinguish among the effects of individual pollutants within air pollution mixtures. Tests on laboratory mice have shown that sulfur dioxide exposure did not affect reproductive function

Only a small number of developmental studies have been done in animals, and of these, in only one study were serious effects on development observed. Developmental studies are designed to determine how a pregnant female's exposure to a chemical might affect the normal processes that take place in her child as it grows (i.e., adverse effects might include a child with learning deficits or problems in social behavior). In one study the offspring of mice who breathed sulfur dioxide during their pregnancy were born small and had some abnormal reflexes. Three other studies in mice and one in rabbits showed no serious effects. Minor variations in the skeleton did occur in the offspring of the rabbits exposed to sulfur dioxide during pregnancy, and delayed bone hardening occurred in the offspring of treated mice. Due in large part to these conflicting results, conclusions about the effects of sulfur dioxide on unborn children cannot be drawn from the available studies.

A study in rats indicated that poor maternal nutrition might cause offspring to be more susceptible later in life to the damage that can occur from breathing sulfur dioxide. In rats, offspring whose mothers were fed a low protein diet while they were pregnant showed greater lung damage from breathing sulfur dioxide when they were older. It is unknown if similar conclusions about human maternal nutrition can be drawn.

It is not likely that parental exposure to sulfur dioxide will cause any changes in a mother's eggs or father's sperm that could affect their unborn children. It is not known if sulfur dioxide or the products to which it is broken down within the body can cross the placenta or accumulate in breast milk; further, it is also unknown whether these resulting breakdown products would be

harmful Accumulation of sulfur dioxide in maternal tissues and then, movement during pregnancy, is unlikely because this compound is water soluble.

Sections 2.6 and 5.6 contain more information about the effects of sulfur dioxide on children.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO SULFUR DIOXIDE?

If your doctor finds that you have been exposed to significant amounts of sulfur dioxide, ask if children may also be exposed. When necessary your doctor may need to ask your State Department of Public Health to investigate.

Because exposure to sulfur dioxide is most likely to occur by breathing contaminated air, families should try to limit their outdoor activities during times of high air pollution. While levels of sulfur dioxide in the air are typically highest during the winter months, human exposure to sulfur dioxide has been shown to be greatest during the summer months. This result is most likely seen because people enjoy being outdoors in warm weather and often leave their household windows open for ventilation.

By paying attention to news bulletins and air pollution advisories, families can control their amount of exposure. The EPA (Environmental Protection Agency) issues the vast majority of air quality alerts. Such warnings might reach the public when ATSDR (Agency for Toxic Substances and Disease Registry) issues a Public Health Advisory and notifies the EPA of a public health threat caused by high levels of atmospheric sulfur dioxide. State and local health and environmental agencies will also be notified and will, in turn, notify their communities. People with respiratory difficulties should pay special attention to these warnings. Additionally, asthmatic children’s outdoor exercise should be limited when high levels of sulfur dioxide are present in the air.

Since exposure to sulfur dioxide occurs primarily through direct breathing of contaminated air, workers in plants where sulfur dioxide occurs as a by-product will not expose their family members at home through residues on their skin or clothes.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SULFUR DIOXIDE?

Sulfur dioxide in the body is changed into other sulfur-containing chemicals in the body. These breakdown products can be found and measured in the blood and urine. However, their measurement requires special equipment which is not routinely available in a doctor's office. Furthermore, exposure to chemicals other than sulfur dioxide can also produce sulfate, so, the presence of sulfate breakdown in your body does not necessarily mean you have been exposed to sulfur dioxide. Lung function tests can be used to examine potential respiratory effects of sulfur dioxide. However, tests of lung function changes cannot determine whether or not you have been specifically exposed to sulfur dioxide because other chemicals can produce similar lung function changes. Chapters 2 and 6 contain further information.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help protect

people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for sulfur dioxide include the following:

The federal government has set regulations to protect individuals from the possible health effects of breathing sulfur dioxide. EPA recommends that the long-term, 1-year average concentrations of sulfur dioxide should not exceed 0.03 ppm. The short-term, 24-hour average concentration should not exceed 0.14 ppm more than once a year. OSHA regulates levels of sulfur dioxide in the workplace. This regulation states that workroom air should contain no more than an average of 2 ppm sulfur dioxide over an 8-hour working shift for 5 consecutive days in a workweek. NIOSH recommends that the average workroom air levels of sulfur dioxide not exceed 2 ppm over a 10-hour period. The 15-minute average exposure in air that should not be exceeded at any time during a workday is 5 ppm. For more information on rules and standards for sulfur dioxide, see Chapter 7.

1.1 0 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: l-800-447- 1544
Fax: (404) 639-6359

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles. contact:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 4874650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of sulfur dioxide. 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.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are 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 (LOAEL) 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.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of sulfur dioxide are indicated in Table 2- 1 and Figure 2- 1.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for sulfur dioxide. 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.

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.

2.2.1 Inhalation Exposure

Table 2-l and Figure 2-l summarize the available quantitative information on the health effects that have been observed in humans and animals following inhalation exposure to sulfur dioxide. All exposure levels are expressed in parts per million (ppm).

2.2.1.1. Death

There have been several case reports of human deaths following acute exposure to high concentrations of sulfur dioxide (Atkinson et al. 1993; Charan et al. 1979; Harkonen et al. 1983; Huber and Loving 1991; Rabinovitch et al. 1989). In most studies, concentrations were not measured. In one study, analysis of gas samples at the time of rescue showed sulfur dioxide concentrations greater than 40 ppm (Rabinovitch et al. 1989). A sulfur dioxide level of 150 ppm was measured during the reenactment of an incident in which a 76-year-old asthmatic woman died of an asthma attack after inhaling vapors from a sulfite-based derusting agent used in her dishwasher (Huber and Loving 1991) Actual sulfur dioxide levels were probably higher since the quantity of derusting agent used in the investigation was approximately 7-10% of the amount originally used by the woman. A concentration of 100 ppm is considered immediately dangerous to life and health (HSDB 1998).

Excess mortality among humans occurred following exposure to high concentrations of sulfur dioxide and suspended particulate matter during acute smog episodes in London during the 1950s (Amdur et al. 1991; Mazumdar et al. 1982; WHO 1979). Peak daily concentrations as high as 4,000 $\mu g/m^3$(1.5 ppm) sulfur dioxide and 6,000 $\mu g/m^3$ of smoke were recorded during some of the pollution episodes. The available evidence suggested that excess mortality may occur at sulfur dioxide levels at or above 500 $\mu g/m^3$ (0.2 ppm) (24-hour mean concentration) in combination with elevated particle levels. The increases in mortality were attributed to bronchitis and other causes of impairment of respiratory function (WHO 1979). Increased mortality from heart disease was also noted. The mortalities occurred mainly among the elderly and among those with pre-existing cardiac and/or respiratory disorders (WHO 1979).

A reanalysis of the mortality and London pollution data revealed that the mortalities were due almost entirely to smoke (Mazumdar et al. 1982). This study applied three types of analyses, including year-by-year multiple regression; stratification using nested quartiles of one pollutant with quantities of the other; and multiple

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (NS)	cont				590 (death in 8 out of 8 rats following an average of 31 hours of exposure)	Cohen et al. 1973
2	Rat (NS)	4hr		593		965 (death in 3 of 8 rats within 2 weeks following exposure)	Cohen et al. 1973
3	Mouse (Swiss Albino)	30 min				3000 (LC_{50})	Hilado and Machado 1977
Systemic							
4	Human-n	10 min	Resp		1-8 (decreased tidal volume; increased respiratory rate)		Amdur et al. 1953
			Cardio		1-8 (increased pulse)		
5	Human-n	1-6 hr	Resp		1M (increased nasal airflow resistance; reduced FEV_1 and FEF_{25-75})		Andersen et al. 1974
6	Human-n	10-30 min	Resp	1	5 (70-75% increased flow resistance after 1 min; cough, sense of irritation)		Frank et al. 1962

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
7	Human-n	5 min	Resp		0.6-0.8 (100% or more increase in specific airway resistance in 13 of 16 subjects)		Islam et al. 1992
8	Human-n	NS	Resp		1 (increased specific airway resistance following deep inhalation of sulfur dioxide)		Lawther et al. 1975
9	Human-n	10min	Resp		5 (increased airway resistance during quiet mouth breathing)		Lawther et al. 1975
10	Human-n	20 min	Resp		8M (erythema of trachea and main bronchi; increase in inflammatory cells in bronchoalveolar lavage fluid)		Sandstrom et al. 1989
11	Human-n	20min	Resp		4 (increased number of lysozyme positive macrophages in bronchoalveolar lavage fluid)		Sandstrom et al. 1989
12	Human-a	1, 3, 5 min	Resp			0.5 (3 min exposure: 173% increase in airway resistance; wheezing, chest tightness, dyspnea)	Balmes et al. 1987

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
13	Human-a	5 min	Resp		0.5 (238% increase in airway resistance during exercising)		Bethel et al. 1983b
14	Human-a	3 min	Resp		0.5 (bronchoconstriction and wheezing when also exposed to cold, dry air)		Bethel et al. 1984
15	Human-a	5 min	Resp		0.25 (134% increased exercise-induced bronchoconstriction)		Bethel et al. 1985
16	Human-a	20 min	Resp		1 M (small increase in total respiratory resistance)		Heath et al. 1994
17	Human-a	10 min	Resp		0.75 M (median concentration that resulted in a 100% increase in specific airway resistance)		Horstman et al. 1986
18	Human-a	30 min	Resp	0.5			Jorres and Magnussen 1990
19	Human-a	50 min	Resp		0.5 (32% increased nasal work of breathing; 60% increased respiratory resistance; decreased $V_{max50\%}$ and $V_{max75\%}$; 24% decreased FEV_1)		Koenig et al. 1985

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
20	Human-a	15 min	Resp	0.1			Koenig et al. 1990
21	Human-a	5 min	Resp	0.2	0.4 (34% increased specific airway resistance)		Linn et al. 1983b
22	Human-a	1 hr	Resp	0.2	0.4 (29% increased specific airway resistance; 2% decreased FEV_1)		Linn et al. 1987
23	Human-a	10-75 min	Resp	0.25 M	0.5 M (2-3-fold increase in specific airway resistance during exercise compared to controls)		Roger et al. 1985
24	Human-a	40 min	Resp	0.5	0.75 (significant increase in airway resistance; decreases in FEV_1, $V_{max50\%}$, $MEF_{40\%(P)}$, and clinical symptoms during moderate exercise)		Schachter et al. 1984
25	Human-a	10 min	Resp		0.1[b] (significant increases in airway resistance during moderate exercise)		Sheppard et al. 1981
26	Rat (Wistar)	8 hr	Resp			800 M (loss of cilia and cell necrosis in trachea and main bronchus)	Stratmann et al. 1991

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
27	Mouse (ICR)	30, 60, 90, 120 min	Resp		20F (degenerative changes to the olfactory epithelium after 16 min of exposure)		Min et al. 1994
28	Gn Pig (NS)	1-3 hr	Resp		2.6 (20% increased resistance and 10% decreased compliance)		Amdur 1959
29	Gn Pig (Hartley)	1 hr	Resp	1 M			Chen et al. 1992b
30	Gn Pig (Perlbright-white)	5d 8hr/d	Resp			5 F (severe destruction of ciliated epithelium and polymorphonuclear infiltrates)	Riedel et al. 1992
31	Dog (NS)	20-40 min	Resp		1.1-141 (5% decreased compliance; 121% increased resistance)		Balchum et al. 1959
32	Dog (NS)	30-40 min	Resp		1.8-148 (8.5% decreased compliance; 150-300% increased resistance)		Balchum et al. 1960b
33	Rabbit (NS)	10-20 min	Resp		200-300F (transient decrease in cough reflex and Hering-Breuer inflation reflex[c])		Hanacek et al. 1991

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Immunological/Lymphoreticular							
34	Gn Pig (Perlbright-white)	5d 8hr/d			5F (increased sensitization to inhalation exposure to ovalbumin)		Riedel et al. 1992
35	Hamster (Golden Syrian)	4 hr			50M (decreased endocytosis by pulmonary macrophage when exposure occurred during exercise)		Skornik and Brain 1990
Reproductive							
36	Mouse (CF-1)	7h/d; Gd6-15		25 F			Murray et al. 1979, 1977
37	Rabbit (New Zealand)	7h/d; Gd6-18		70 F			Murray et al. 1979, 1977
Developmental							
38	Mouse (CF-1)	7h/d; Gd6-15			25 (reduced fetal weight and increased skeletal variations)		Murray et al. 1979, 1977
39	Mouse (CD-1)	Gd7-18				32 (increased time for the righting reflex and negative geotaxis)	Singh 1989

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
40	Rabbit (New Zealand)	7h/d; Gd6-18			70 (increased skeletal variations)		Murray et al. 1979, 1977
INTERMEDIATE EXPOSURE							
Systemic							
41	Rat (Buffalo)	12 wk; 5d/wk; 1h/d	Resp		30M (inflammation of bronchial mucosa)		Krasnowska et al. 1998
42	Rat (NS)	3hr/d; 5d/wk; 2-42 d	Resp		400 (epithelial necrosis, loss of cilia, and increased numbers and activity of goblet cells)		Lamb and Reid 1968
43	Hamster (Syrian)	19-74 days; 5 d/wk; 4 hr/d	Resp		650 (dilated bronchi and alveolar ducts; small scattered areas of focal emphysema)		Goldring et al. 1970
44	Rabbit (New Zealand)	5 wk 6 d/wk 2 hr/d	Resp			70-300 M (decreased respiratory rate; rhinitis; tracheitis; bronchopneumonia)	Miyata et al. 1990
			Bd Wt		70-300M (body weight gain 25% less than controls)		
Immunological/Lymphoreticular							
45	Gn Pig (Hartley)	6 wk 5 d/wk 4 hr/d				5 M (increased delayed-type dyspneic symptoms after challenge by *C. albicans* resulting in 3/12 guinea pigs dying)	Kitabatake et al. 1995

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Neurological							
46	Mouse (CD-1)	24 d; continuous		12 F	30 F (transient changes in the frequency of various activity-exploration behaviors)		Petruzzi et al. 1996
Reproductive							
47	Mouse (CD-1)	24 d; continuous		30			Petruzzi et al. 1996
Developmental							
48	Mouse (CD-1)	24 d, continuous		30			Petruzzi et al. 1996
CHRONIC EXPOSURE							
Systemic							
49	Monkey (Cynomol-gus)	78 wk 7 d/wk 23.3 hr/d	Resp	5.1			Alarie et al. 1975
			Cardio	5.1			
			Hemato	5.1			
			Hepatic	5.1			
			Renal	5.1			
			Bd Wt	5.1			

Table 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
50	Gn Pig (Hartley)	52 wk; 7 d/wk; 22 wk; 22 hr/d	Resp	5.7					Alarie et al. 1972
			Cardio	5.7					
			Hemato	5.7					
			Hepatic	1.0	5.7	(increase in the size of hepatocytes accompanied by cytoplasmic vacuolation)			
			Renal	5.7					
			Bd Wt	5.7					
Cancer									
51	Mouse LX	2 yr 5 d/wk 5 min/d					500	(CEL: lung adenomas in 28/58 male and female mice; lung carcinomas in 4/30 females)	Peacock and Spence 1967

[a]The numbers correspond to entries in Figure 2-1.

[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.01 ppm; the minimal LOAEL of 0.1 ppm was divided by an uncertainty factor of 9 to account for human variability and use of a minimal LOAEL.

[c]The Hering-Breur reflex involves reaction of the lung to inflation. Inflation of the lung inhibits inspiration and brings on expiration.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = female; FEF = forced expiratory flow during the middle half of the expired volume; FEV_1 = forced expiratory volume in one second; Gd = gestation day; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); Human-a = asthmatic human; Human-n = nonasthmatic human; LOAEL = lowest-observed-adverse-effect level; M = male; $MEF_{40\%\,(P)}$ = maximal expiratory flow at 60% of vital capacity below total lung capacity on the partial flow volume curve; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; $V_{max50\%}$ = maximal flow at 50% of the vital capacity; $V_{max75\%}$ = maximal flow at 75% of the vital capacity; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation

Acute (≤14 days)

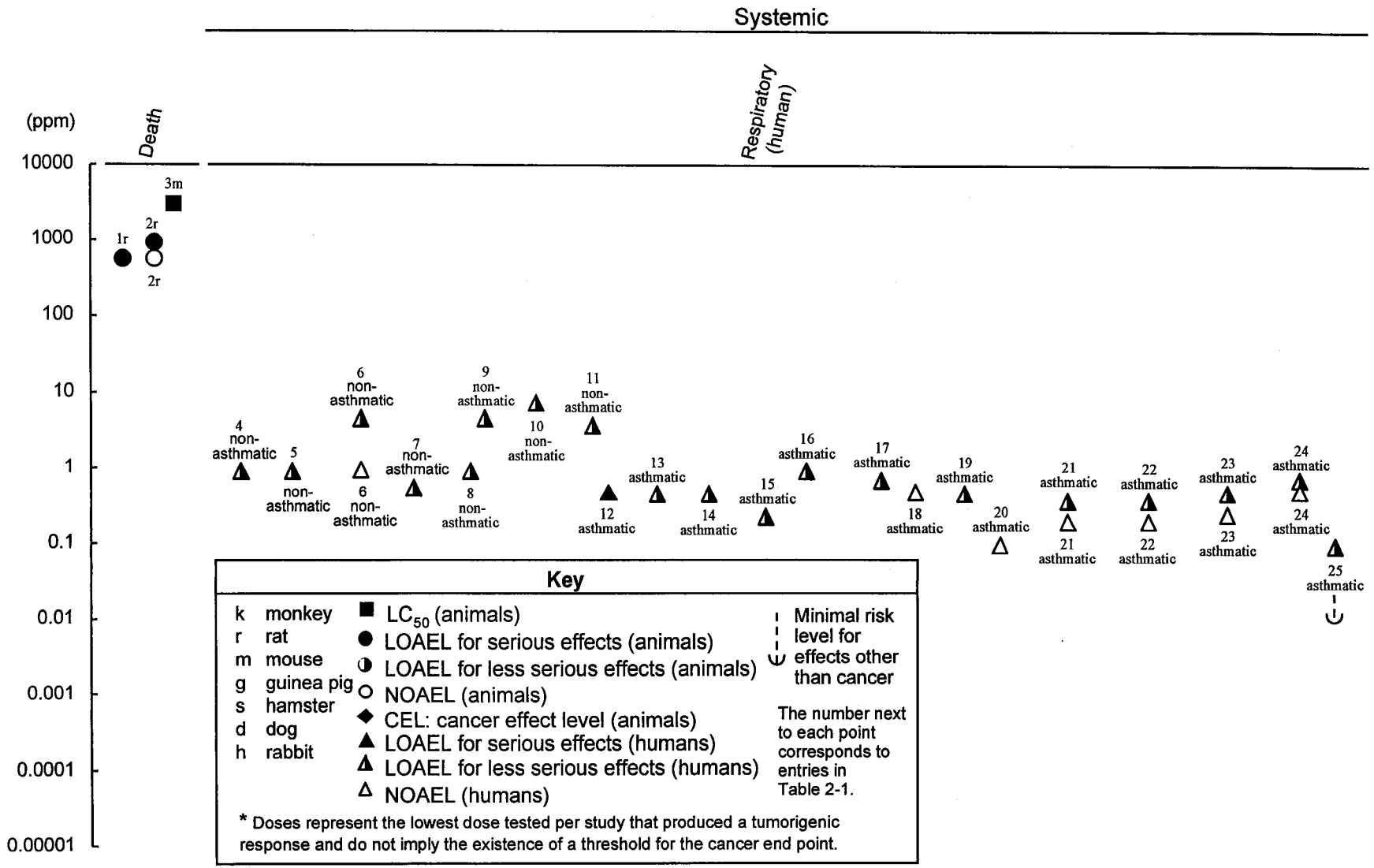


Figure 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (cont.)

Acute (≤14 days)

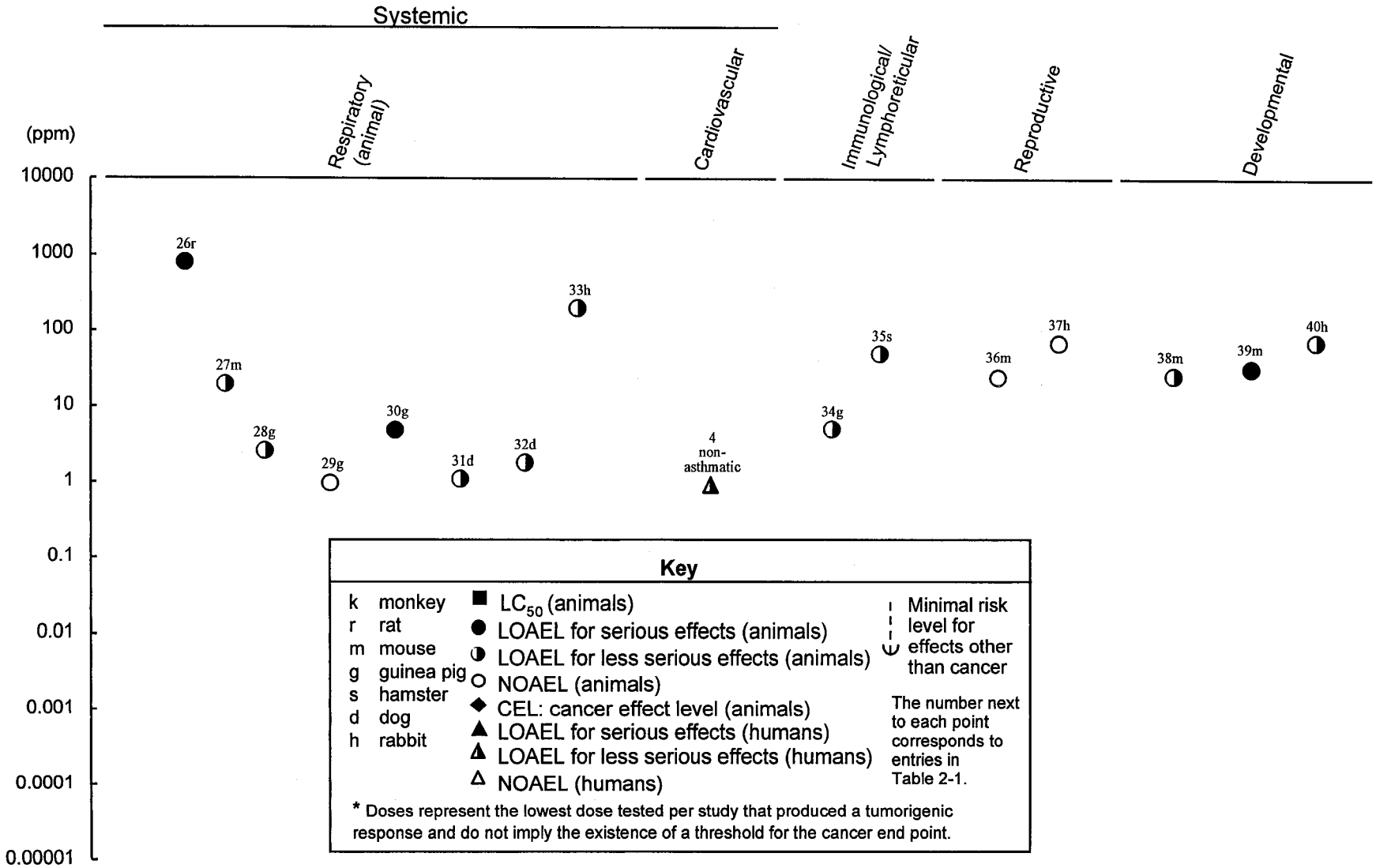


Figure 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (cont.)

Intermediate (15-364 days)

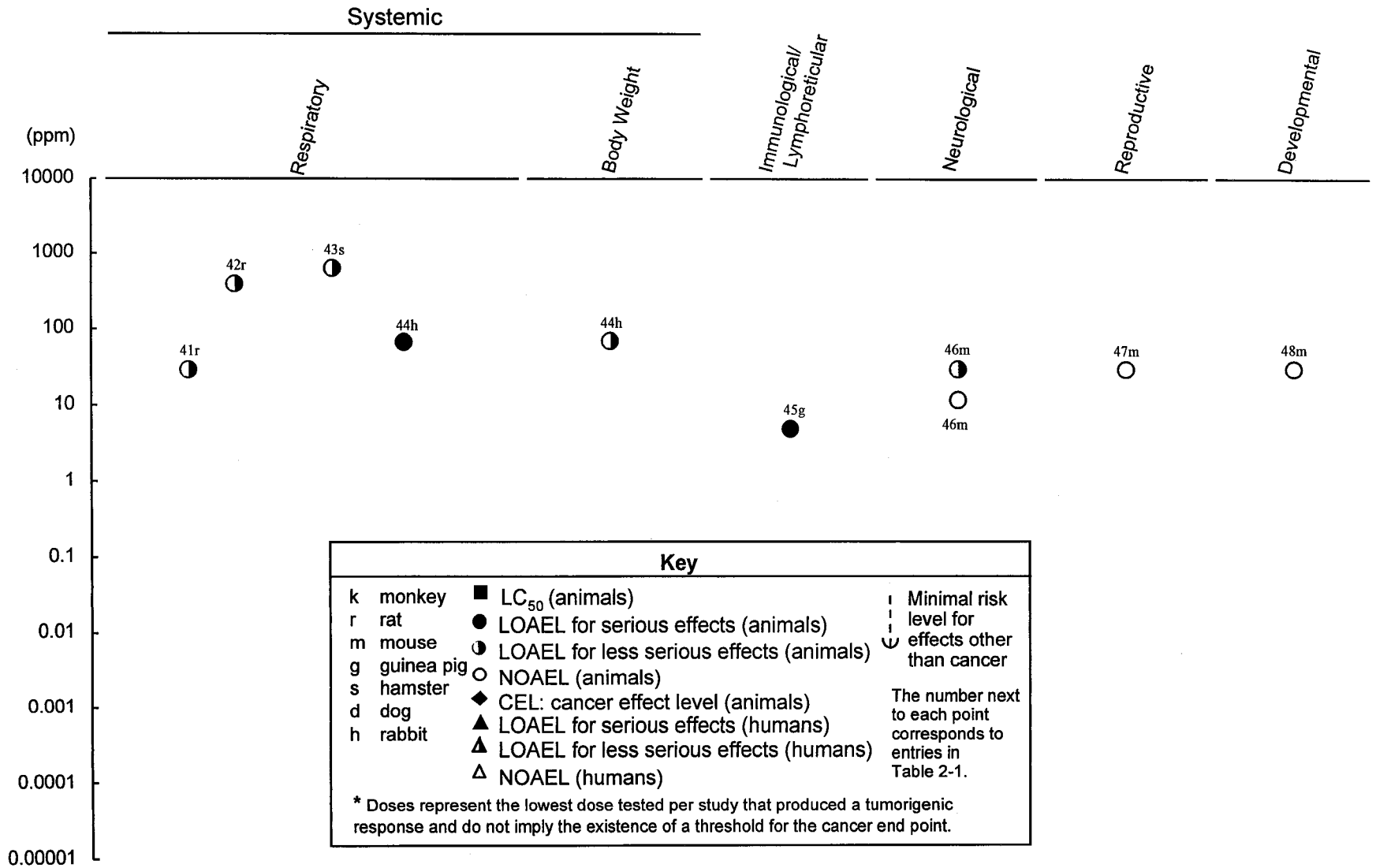
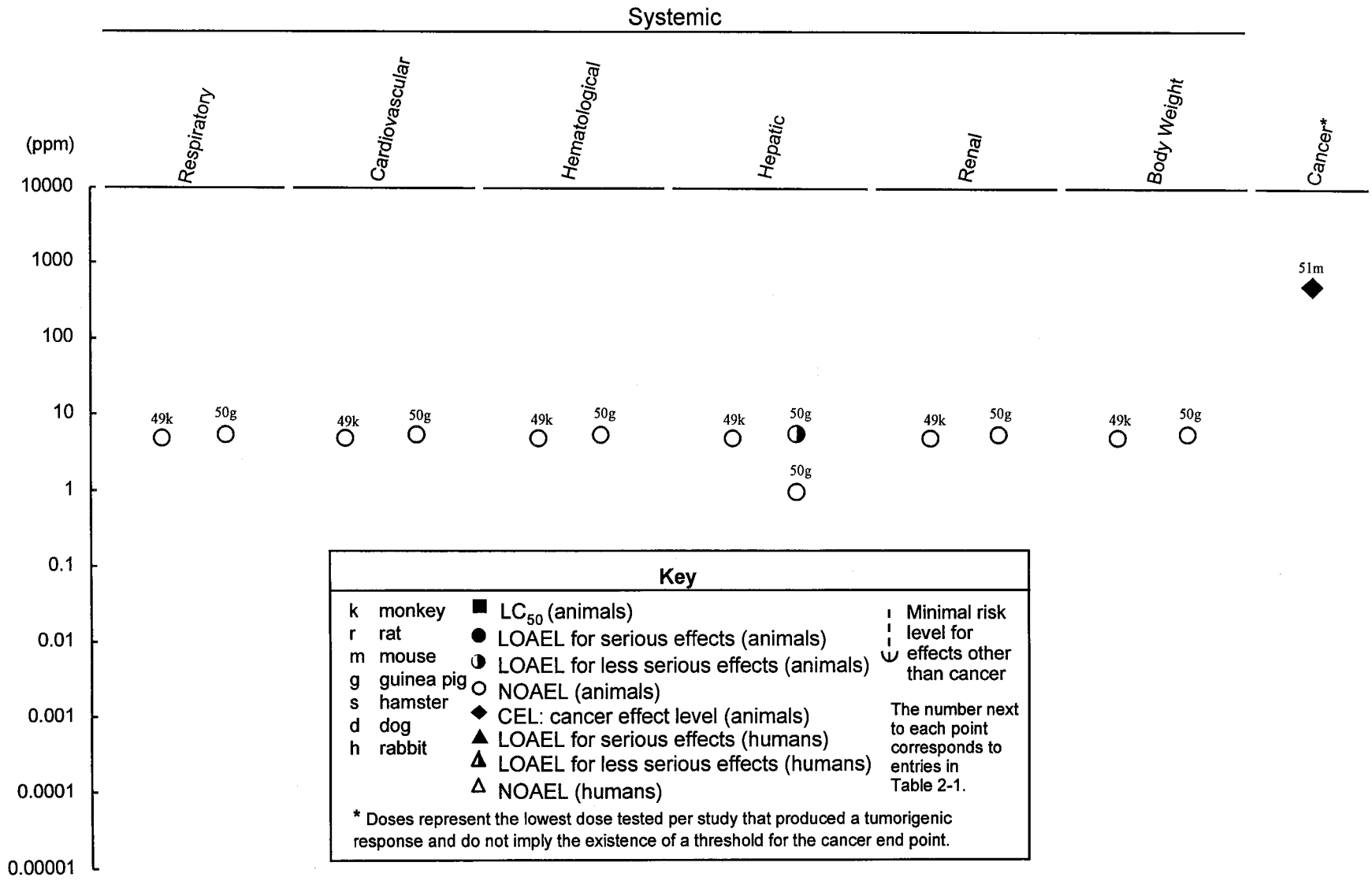


Figure 2-1. Levels of Significant Exposure to Sulfur Dioxide - Inhalation (cont.)

Chronic (≥365 days)



regression of a special subset of high-pollution days. However, a later reexamination of mortality and London pollution data revealed that the log of acid aerosol concentrations was more strongly associated with raw total mortality in bivariate analyses than with smoke or sulfur dioxide (Thurston et al. 1989).

Associations have also been reported between daily acute mortality and pollution episodes involving sulfur dioxide and suspended particulate matter in Philadelphia, PA, (1973-1988) and Steubenville, OH, (1974-1984) (Moolgavkar et al. 1995a, 1995b). Although the mortality has been attributed to the particulate component of air pollution, recent reanalyses of data have indicated that it is premature to single out one specific component as being responsible for the observed association between air pollution and mortality (Moolgavkar et al. 1995a, 1995b, 1996).

In eastern and western Europe, associations between short-term increases in air pollutant levels and daily mortality rates have recently been evaluated by the Air Pollution and Health: a European Approach (APHEA) project (Katsouyanni et al. 1997). The purpose of the project was to provide a standardized method of evaluation between 15 European cities, and the primary pollutants examined were sulfur dioxide and particulates. Effects were evaluated for both current day increases in air pollution levels and for lag periods of 1-5 days past exposure. Statistical techniques were used to control for confounding factors such as various air pollutants, temperature, relative humidity, influenza epidemics, season, year, month, holidays, and day of the week. Despite efforts to ensure consistency in evaluation methods, the sulfur dioxide findings were variable. For instance, an association between short-term increases of sulfur dioxide levels in air and increased daily mortality was not observed in some cities (Bacharova 1996; Ballester et al. 1996; Verhoeff et al. 1996). In another city, analysis of sulfur dioxide alone indicated an association with daily mortality, but the effect was not observed when sulfur dioxide was analyzed in combination with other air pollutants (Anderson et al. 1996). Weak but significant associations between short term increases in sulfur dioxide levels and daily mortality were noted in other cities (Spix and Wichmann 1996; Sunyer et al. 1996; Touloumi et al. 1996).

Results from the pooling and metaanalysis of data from 12 cities suggested a weak but statistically significant association between increased sulfur dioxide levels and daily mortality in western European cities but not in central eastern Europe (Katsouyanni et al. 1997). In most studies sulfur dioxide concentrations were highest during the winter, but effects were noted primarily during the summer. A possible explanation may be an increased exposure to outdoor air during the summer months (Sunyer 1996).

Inconsistencies in the various APHEA studies may have resulted from several limitations with epidemiological studies of air pollutant mixtures. For example, there may be confounding effects due to air pollutants that were not measured. Also, concentrations were obtained from monitoring sites and this provides no information about personal exposures within individuals of a population. Lastly, there is little understanding about the mechanism of toxicity associated with air pollutants. Therefore, separating the effects of individual air pollutants within a mixture is very unlikely with the technology available at this time (Ballester et al. 1996; Katsouyanni et al. 1997; Loomis et al. 1996; Moolgavkar et al. 1996).

The approximate LC_{50} for a 30minute exposure in Swiss albino mice was 3,000 ppm (Hilado and Machado 1977). In this study, there were no deaths during or after 30 minutes of exposure to 1,190 ppm sulfur dioxide. However, the study is limited because it did not indicate the age, sex, or the number of animals used in the experiment. The LC_{50} value associated with death in mice is shown in Table 2-1 and plotted in Figure 2- 1.

The time course of mortality in groups of 8 rats was examined following continuous exposure to 590-500,000 ppm sulfur dioxide (Cohen et al. 1973). Average mortality times were 1866,750, 176, <10 and <2 minutes for rats exposed to 590,925,2350,50,000, or 500,000 ppm sulfur dioxide respectively. Mortality in groups of 8 rats was monitored for two weeks following a 4-hour exposure to 224-1,319 ppm sulfur dioxide (Cohen et al. 1973). None of the rats died following exposure to 224 or 593 ppm sulfur dioxide. Three rats exposed to 965 ppm died. Five rats exposed to 1,168 ppm died 1 to 48 hours after exposure, and all rats exposed to 1,3 19 ppm died 1 to 24 hours after exposure. Results of these studies are illustrated in Table 2- 1 and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

Respiratory Effects. In humans, and in particular asthmatics, respiratory changes are a primary response following acute exposure to sulfur dioxide. Numerous controlled clinical studies have examined pulmonary lung function, usually assessed by measurement of increases in specific airway resistance and/or decreases in forced expiratory volume or forced expiratory flow, in human subjects exposed to sulfur dioxide. The methods of exposure to sulfur dioxide usually involved oronasal, nose-only, or mouth breathing techniques. Several chamber studies have been performed in a number of investigations in various laboratories.

In 10 healthy, nonasthmatic individuals, exposure to sulfur dioxide (via a chamber) at concentrations of up to 1 .0 ppm for up to 40 minutes was associated with only a slight increase in subjective, mild, upper-respiratory symptoms such as sore throat and ability to taste and smell sulfur dioxide (Schachter et al. 1984). There was no effect on lung function parameters. However, reductions in forced expiratory volume and forced expiratory flow and an increase in nasal airflow resistance were observed in 15 healthy subjects exposed nose-only to ≥1.0 ppm sulfur dioxide for 1-6 hours (Andersen et al. 1974). Decreased tidal volume and increased respiratory rate were observed in 14 healthy subjects exposed to 1-8 ppm sulfur dioxide for 10 minutes (Amdur et al. 1953). Specific airway resistance was increased in 26 healthy individuals exposed to 0.6-0.8 ppm sulfur dioxide for 5 minutes (Islam et al. 1992). A significant decrease in nasal mucus flow was seen in 15 healthy subjects at 5 and 25 ppm sulfur dioxide (Anderson et al. 1974). Reduced bronchial clearance was observed at 5 ppm (Wolff et al. 1986). Exercise increased the rate of bronchial clearance (Wolff et al. 1986). Increased airway resistance during rest was observed in 7 healthy subjects exposed to 4-6 ppm sulfur dioxide in a body plethysmograph for 10 minutes (Nadel et al. 1965). When 11 healthy subjects were exposed mouth only to 5 ppm sulfur dioxide for 10-30 minutes, increased flow resistance was noted (Frank et al. 1962). Cough, a sense of irritation, and increased salivation were also seen at 5 ppm. No effects were observed at 1 ppm. Erythema of the trachea and main bronchi was seen in 22 healthy individuals exposed to 8 ppm sulfur dioxide for 20 minutes (Sandstrom et al. 1989a, 1989b). This effect was accompanied by an increase in inflammatory cells in bronchoalveolar lavage fluid. Increased numbers of inflammatory cells were also observed in the bronchoalveolar lavage fluid in groups of 4-10 subjects exposed to 4 ppm sulfur dioxide for 20 minutes (Sandstrom et al. 1989a, 1989b).

A series of inhalation exposure studies were conducted in healthy subjects with various concentrations of sulfur dioxide (Lawther et al. 1975). Pulmonary function changes were not observed in 13 subjects following quiet nasal breathing of 1 ppm sulfur dioxide for 1 hour. However, significant increases in specific airway resistance were noted in 12 subjects who inhaled 25 deep breaths of 1 ppm sulfur dioxide. Increases in specific airway resistance were also noted after the subjects took 25 deep breaths of filtered air, but the response was greater with sulfur dioxide exposure. In 17 subjects, significant increases in specific airway resistance were observed after inhaling 16 deep breaths of filtered air. Additional dose-related increases in resistance were observed after inhaling 8, 16, and 32 deep breaths of 3 ppm sulfur dioxide. Specific airway resistance increased significantly in 14 subjects who breathed 5 ppm sulfur dioxide quietly by mouth for 10 minutes. Resistance was highest immediately after exposure and, depending on the sensitivity of the subject, lasted from 5 to 65 minutes following exposure. Additional dose-related increases in resistance were not

observed following exposure to l0-30 ppm sulfur dioxide. Subjects could detect higher levels of sulfur dioxide and it appears that they tried to protect themselves with shallow breathing.

The results of controlled laboratory studies in humans have established that asthmatics are particularly sensitive to the respiratory effects of sulfur dioxide. In a study of 21 asthmatics exposed for 10 minutes to sulfur dioxide by mouthpiece while at rest, increases in airway resistance were observed at 1,3, and 5 ppm (Sheppard et al. 1980).

Controlled studies have indicated that the pulmonary effects of sulfur dioxide can be significantly enhanced by exercise. Significant increases in airway resistance have been clearly demonstrated in moderately exercising asthmatics (ventilation range: 35-60 L/minute) exposed briefly (3-10 minutes) to 0.40-1.0 ppm sulfur dioxide (Bethel et al. 1985; Linn et al. 1983a, 1984a; Roger et al. 1985; Schachter et al. 1984). Significant changes in airway resistance were observed in young adult mild asthmatics exposed, while exercising, to a concentration of sulfur dioxide as low as 0.25 ppm through a mouthpiece (Sheppard et al. 1981). The two most sensitive asthmatics exhibited some degree of bronchoconstriction, as evidenced by a slight increase in specific airway resistance (SR_{aw}) following inhalation of 0.1 ppm sulfur dioxide through a mouthpiece for 10 minutes (Sheppard et al. 1981). A dose-response relationship, as measured by airway resistance, was observed in the two sensitive subjects following exposures to 0.25 and 0.5 ppm sulfur dioxide. At 0.25 ppm, the difference between baseline specific airway resistance and specific airway resistance (ΔSR,) after inhalation of sulfur dioxide was approximately 5 Lxcm H_2O/L/s (units of SR_{aw}). At 0.5 ppm, the ΔSR_{aw} exceeded 15 Lxcm H,O/L/s.

Lung function changes in asthmatics exposed by inhalation to 0.25 ppm sulfur dioxide have been reported by other investigators. In a chamber study of moderately exercising asthmatics, the concentration of sulfur dioxide required to produce an increase in airway resistance 100% greater than the response to clean air [designated as $PC(SO_2)$] has been determined (Horstman et al. 1986). Analysis of the cumulative percentage of subjects plotted as a function of $PC(SO_2,)$ revealed that 25% of the subjects exhibited a $PC(SO_2)$ of 0.25-0.5 ppm sulfur dioxide. The study authors suggested that the 25% of the mild asthmatics who were very sensitive to sulfur dioxide could possibly exhibit bronchoconstriction if they were to perform normal exercise routines in some highly industrialized areas of the United States. Increases in specific airway resistance were observed in 9-19 moderately exercising asthmatics exposed oronasally to 0.25 ppm sulfur dioxide for 5 minutes (Bethel et al. 1985). A dose-related increase in specific airway resistance was seen in

asthmatics following a 3-minute exposure (via mouthpiece) to ≥ 0.25 ppm sulfur dioxide (Myers et al. 1986a, 1986b).

Some studies of asthmatics have reported a lack of significant lung function changes in asthmatics following exposures to 0.1-0.5 ppm (Jorres and Magnussen 1990; Koenig et al. 1990). Bronchoconstrictive responses to sulfur dioxide are highly variable among individual asthmatics (Horstman et al. 1986). In some studies, asthmatics were preselected for sensitivity to sulfur dioxide and this may explain the range of sulfur dioxide-induced responses obtained by different investigators.

In addition to exercise, sulfur dioxide-induced bronchoconstriction can be increased by cold or dry air (Sheppard et al. 1984). For instance, the concentration resulting in a 100% increase in specific airway resistance in 8 asthmatics exposed to sulfur dioxide in dry, cold air was 0.51±0.2 ppm, whereas it was 0.6±0.41 ppm for dry, warm air and 0.87±0.41 ppm humid, warm air.

In several controlled acute studies, the authors have reported that, because of the severity of the pulmonary response, exposures to sulfur dioxide had to be terminated for some of the asthmatic subjects while other subjects required medical attention. Two out of seven asthmatics required a bronchodilator after exposure to cold air and 0.5 ppm sulfur dioxide (Bethel et al. 1984). Two of 10 subjects exposed to 0.5 ppm sulfur dioxide were unable to complete the experiment (Koenig et al. 1985). Similar events were reported by other investigators (Balmes et al. 1987; Horstman et al. 1986, 1988; Linn et al. 1984a, 1984b, 1984c; Roger et al. 1985).

Controlled studies in asthmatic subjects have demonstrated that repeated exposures to sulfur dioxide reduce the responsiveness of asthmatics to the chemical. For instance, the pulmonary response of 10 exercising asthmatics exposed to 1.0 ppm sulfur dioxide in a chamber was attenuated after repeated exercise (Kehrl et al. 1987). Bronchoconstriction was less severe in 14 exercising asthmatics exposed to 0.6 ppm sulfur dioxide on the second day of a 2-day exposure period (Linn et al. 1984a). Specific airway resistance in 28 asthmatics was significantly less after second and third exercises when compared with the first exercise (Roger et al. 1985).

A series of studies was conducted to examine respiratory function in healthy, atopic, or asthmatic adolescents (n=8-9, aged 12-17 years) and 10 healthy male seniors (aged 55-73 years) following exposure by mouth only to a mixture of 1 ppm sulfur dioxide and 1 mg/m^3 sodium chloride aerosol (Koenig et al. 1982a, 1982b,

1983; Rondinelli et al. 1987). Exposures consisted of 30 minutes of rest and 10 minutes of exercise for adolescents and 20 minutes of rest and 10 minutes of exercise for seniors. Statistically significant decreases in forced expiratory volume in 1 second (FEV,) were observed in all groups of subjects following exposure to the sulfur dioxide and sodium chloride mixture during exercise. The magnitude of decreases were 23% in asthmatic adolescents, 18% in atopic adolescents, 8% in seniors, and 6% in healthy adolescents (Koenig et al. 1982a, 1982b, 1983; Rondinelli et al. 1987). Based on a comparison of FEV_1 values, it was concluded that respiratory health status and not age is the primary factor in determining susceptibility to sulfur dioxide (Rondinelli et al. 1987). Asthmatic adolescents were most sensitive to sulfur dioxide and normal adolescents were least sensitive. Responses in seniors and healthy adolescents were similar. However, the doses inhaled by healthy adolescents were about 20% greater because of a longer exposure period and a more strenuous exercise period. A further decrease in FEV_1 may have occurred in seniors had they received the same doses as adolescents. In two of the studies, it was verified that exposure to a mixture of sulfur dioxide and sodium chloride aerosol resulted in effects which did not differ significantly from those obtained from exposure to sulfur dioxide alone (Koenig et al. 1982b, 1982a). The authors stated that in the environment sulfur dioxide occurs together with one or more droplet aerosols and that the studies represented a realistic exposure scenario.

Adaptation to irritant concentrations of sulfur dioxide is a recognized occurrence in workers (Department of Labor 1975). The potential tolerance to the pulmonary effects of sulfur dioxide has been studied in asthmatics. Eight asthmatic subjects were exposed to 0.5 ppm sulfur dioxide with a mouthpiece for 3 minutes while performing voluntary eucapnic kyperpnea (rapid deep breathing to deplete arterial carbon dioxide) (Sheppard et al. 1983). The subjects received three 3minute exposures with a 30 minute rest period between exposures. Specific airway resistance was increased significantly more after the first exposure to sulfur dioxide than after the second or third exposures. Tolerance was not observed when the exposures were repeated 24 hours later and then 7 days later.

A case study describes a sulfide dust explosion in a copper mine that liberated large amounts of sulfur dioxide (Rabinovitch et al. 1989). Analysis of the gas sample obtained at the time of rescue showed sulfur dioxide concentrations >40 ppm, with no other toxic gases present. Effects resulting from the exposure consisted of burning of the nose and throat, dyspnea, and severe airway obstruction that was only partially reversed 2 years after the exposure. In another case report of an industrial accident at a paper mill involving exposure to high but unmeasured concentrations of sulfur dioxide, histological examination of the lungs of two subjects who died revealed extensive sloughing of the mucosa of large and small airways along with

hemorrhagic alveolar edema. Acute symptoms observed in the survivors included irritation of the nose and throat, tightness in the chest, and intense dyspnea. Serial pulmonary function tests revealed severe airway obstruction in one subject on the first day of examination Another survivor who used a protective mask developed mild airway obstruction by day 116. No pulmonary function abnormalities were noted in the third survivor, a fireman who arrived later on the scene.

Bronchial hypersensitivity can develop following a single exposure to very high concentrations of sulfur dioxide, a syndrome referred to as reactive airway dysfunction syndrome or RADS (Brooks et al. 1985; Brooks 1992; Brooks et al. 1985; Goldstein et al. 1979; Harkonen et al. 1983). In this syndrome, the bronchial epithelial damage results in increased sensitization and nonspecific hypersensitivity to a wide range of other irritant stimuli.

Bronchitis has been reported in pulp mill workers following brief accidental exposures to 100 ppm sulfur dioxide (Skalpe 1964).

Epidemiological studies on the relationship between sulfur dioxide exposure and respiratory effects have been conducted. However, these studies are limited because of the difficulties in separating potential effects of sulfur dioxide from those of particulates and other air pollutants. A longitudinal study of 343 children exposed to sulfur dioxide and particulate sulfate was conducted in three towns in Arizona, two of which have smelters (Dodge et al. 1985). The study period was from 1979 to 1982. The annual average sulfur dioxide concentrations at two monitoring sites were 0.005 ppm and 0.04 ppm. However, in the area of highest pollution, children were exposed intermittently to high levels of sulfur dioxide (peak 3-hour mean exceeded 1 ppm) and moderate levels of particulate sulfate. A significant correlation between the prevalence of cough and pollution levels was noted. There were no significant changes in lung function over a 3-year period.

Lung function has been studied in 200 school-age children following several acute air pollution episodes in Steubenville, OH (Dockery et al. 1982). One day in 1979, the children were exposed to mean daily concentrations of go.17 ppm sulfur dioxide and 0.27 mg/m^3 total suspended particles, levels which exceeded the 24-hour standard in 1979. The children were examined in three weekly visits following each pollution alert. The children were measured again in five weekly examinations in the spring and fall of 1980. Slight (2-3%) decreases in forced vital capacity (FVC) and forced expiratory volume in 0.75 seconds ($FEV_{0.75}$) were noted in the children the day following the acute pollution episode in 1979 and 1-2 weeks later. The

decreases were statistically significant and reversible after 2-3 weeks. The effects of total suspended particles cannot be separated from those of sulfur dioxide.

In New York, the association between seasonal air pollution levels and forced expiratory volume in 0.75 seconds ($FEV_{0.75}$) was examined in two age groups of children (5-8 and 9-13 years-old) (Shy et al. 1973). At the time of the study, sulfur dioxide levels in polluted areas ranged from 63-71 μg/m^3 (0.024-0.027 ppm) and levels of total suspended particulates (TSPs), suspended sulfates, and nitrogen dioxide were elevated in comparison to non-polluted areas Levels of sulfur dioxide, TSPs, and suspended sulfates were greatly reduced three years prior to the initiation of the study. Previous sulfur dioxide levels ranged from 364-435 μg/m^3 (0.14-0.17 ppm). Associations between pollutant levels and reduced $FEV_{0.75}$ were only observed in the older group of children. The authors concluded that persistent respiratory effects may result from 5-10 year exposures to high air pollution levels during early childhood. Effects associated with individual air pollutants were not separated in this study.

The association between peak expiratory flow rates (PEFR) and sulfur dioxide and particulate air pollution was examined in 60 asthmatic children (aged 9-14 years) living in Budapest during the period of September 13 through December 5, 1993 (Agocs et al. 1997). Sulfur dioxide concentrations ranged from 11-185 μg/m^3 (0.004-0.071), and levels exceeded World Health Organization (WHO) limits on several days. Confounding effects such as temperature, humidity, weekday, and time trends were controlled and each air pollutant was assessed individually. There were no consistent associations between air pollution levels and PEER. Study limitations were addressed by the authors and included medication use by many of the children, incomplete control of seasonal factors, and a lack of personal exposure data.

In London, increases in sulfur dioxide levels by 14 μg/m^3 (0.005 ppm) were associated with a 12% increase in the number of emergency room visits for wheezing episodes in children (Buchdahl et al. 1996). Confounding effects from season, temperature, and wind speed were controlled, but effects from the other air pollutants, including ozone and nitrogen dioxide, were not separated. In the evaluation of ozone, effects from sulfur dioxide and nitrogen dioxide were controlled, and ozone was found to have the strongest association with wheezing episodes in children.

Difficulty breathing and cough were reported by 91-94% of workers in a Yugoslavian broom manufacturing plant who were exposed to average sulfur dioxide concentrations of 0.29 and 57 ppm in the summer and winter, respectively (Savic et al. 1987). There appeared to be no control for confounding factors such as

occupational exposure to dust and smoking. A study was also conducted of workers exposed to sulfur dioxide in a refrigerant manufacturing plant (Kehoe et al. 1932). Prior to 1927 concentrations of sulfur dioxide averaged between 80-100 ppm. After the installation of a ventilation system, sulfur dioxide levels typically ranged between 5-35 ppm with occasional peaks as high as 50-70 ppm. The incidence of respiratory irritation and shortness of breath during heavy activity were significantly increased in 100 exposed workers. Chest X-rays revealed no differences between exposed and unexposed workers at the same plant Occupational exposure to other chemicals was not described and there was no control for smoking.

A significant decrease in forced expiratory volume in 1 second (FEV,) was observed in 113 workers exposed to $\geq$1 ppm sulfur dioxide for an unspecified time in a copper smelter in Salt Lake City (Smith et al. 1977). Smoking status was assessed in the study. However, workers were also exposed to respirable dust. A study conducted years later at the same copper smelter found no significant relationships between pulmonary function and exposure to $\geq$5 ppm sulfur dioxide in 430 workers (Lebowitz et al. 1979). Exposure durations ranged from 0 to >20 years and confounding factors such as age, smoking, and exposure to dust were corrected. The authors suggested that the previous findings of Smith et al. (1977) may have resulted from limitations of the study, such as a small sample size and inadequate correction for age.

In another study of 953 copper smelter workers in Garfield, Utah, a significant reduction in FVC and FEV_1 was associated with long-term (>20 years) exposure to 0.4-3.0 ppm sulfur dioxide (Archer and Gillan 1978). Smoking status was assessed in the study. The reduction was observed with increasing duration of exposure in both smokers and nonsmokers but was not observed in controls. However, workers were also exposed to arsenic, copper, manganese, iron, and other trace metals.

Workers (4,506 and 5,943) exposed to mean concentrations of approximately 0.84-1.2 ppm sulfur dioxide for an unspecified time period at two British steel plants did not experience an increase in respiratory symptoms or reduction in respiratory performance (Lowe et al. 1970). Confounding factors such as smoking and occupational exposure to dust were controlled.

In a study of 56 workers exposed to 2-36 ppm sulfur dioxide in pulp mills for 1 month to 40 years, cough was reported by 56% of workers, sputum production by 46%, and difficulty breathing by 22% (Skalpe 1964). Symptoms were reported in higher percentages by workers $\leq$50-years-old. Maximal expiratory flow rate was significantly reduced in workers <50-years-old. The author speculated the most likely reason for increased

effects in the younger workers was that minor respiratory effects are more likely detected due to decreased prevalence of respiratory symptoms at a younger age. Occupational exposure to other chemicals was not reported but smoking status was controlled.

Variability in the findings of occupational studies may have resulted from common limitations in each study. Personal exposure levels were not measured in any of the studies but were estimated from area samples. Levels of sulfur dioxide may vary widely within a small area of a plant and exposures could differ significantly between workers in the area. Also, workers are usually exposed to multiple toxic substances and it is difficult to separate the effects of individual compounds.

Though erratic results were obtained in the occupational studies, it is evident that effects occurred at higher concentrations than in controlled chamber studies of asthmatics. Workers represent a subgroup which is healthier than the general population. Due to breathing difficulties, individuals with respiratory disorders such as asthma would generally be excluded from working in areas with high sulfur dioxide concentrations. Therefore, it is expected that changes in lung function would be observed at lower concentrations in controlled studies of asthmatics than in occupational studies.

Studies in experimental animals have supported the findings of pulmonary effects of sulfur dioxide in humans following inhalation exposure. Sixteen guinea pigs exposed to 2.6 ppm sulfur dioxide in an exposure chamber for 1 hour showed a 20% increase in resistance accompanied by a 10% decrease in compliance (Amdur 1959). The response to sulfur dioxide increased when exposure was increased to 3 hours. Increased pulmonary flow resistance was noted in guinea pigs exposed to 0.16-835 ppm sulfur dioxide (Amdur 1966). In a nose-only inhalation exposure study, 6-9 guinea pigs exposed to 1 .0 ppm sulfur dioxide for 1 hour did not display any effects on airway responsiveness (Chen et al. 1992b). In a study designed to assess the bronchial sensitization to ovalbumin in 6 guinea pigs following exposure to 5 ppm sulfur dioxide for 6 hours per day for 5 days, serious pulmonary effects, including severe destruction of ciliated epithelium of the bronchioles, partial collapse of alveoli, and polymorphonuclear infiltrates were observed (Riedel et al. 1992).

Decreased compliance and increased resistance were noted in 12 anesthetized dogs exposed to 1.1-141 ppm sulfur dioxide for 2040 minutes using a mask fitted so that the dogs breathed through the nose and the mouth (Balchum et al. 1959). The average decrease in compliance for 11 dogs was 5%. One dog exposed to 141 ppm for 40 minutes displayed a 121% decrease in compliance. Dogs exposed to 45 ppm for 16 minutes displayed increased resistance and decreased compliance of the lung (Balchum et al. 1960b). Decreased

compliance and increased resistance were also seen in 10 anesthetized dogs exposed to 1.8-148 ppm sulfur dioxide through a tracheal cannula (Balchum et al. 1960b). Compliance was decreased from control levels at an average of 8.5% (statistically significant at $p<0.05$). Resistance was increased by 150-300%. The increase in resistance occurred within 9 seconds after the onset of sulfur dioxide exposure and disappeared quickly at the end of exposure.

Acute-duration exposure to high concentrations of sulfur dioxide can result in biochemical, clinical, and histological changes in the respiratory systems of the mouse and the rabbit. A transient decrease in cough reflex and the Hering-Breuer inflation reflex were observed in 18 rabbits exposed to 200-300 ppm sulfur dioxide for 10-20 minutes (Hanacek et al. 1991).

Four mice exposed to 20 ppm sulfur dioxide for up to 120 minutes exhibited degenerative changes in the olfactory epithelium (Min et al. 1994). A substantially increased number of polymorphonuclear lymphocytes in the trachea was noted in 3-5 rats exposed to 230 ppm sulfur dioxide for 5 hours (Farone et al. 1995). A loss of cilia and cell necrosis in the trachea and main bronchus were observed in 5 rats exposed to 800 ppm sulfur dioxide for 8 hours (Stratmann et al. 1991).

Rats exposed to 25 ppm sulfur dioxide for up to 5 days displayed nasal epithelial metaplasia and basal cell hyperplasia (Fowlie et al. 1990).

Respiratory effects from exposure to sulfur dioxide for intermediate time periods have also been studied in animals. Mild bronchitic lesions were seen in 72 hamsters exposed to 650 ppm sulfur dioxide for 4 hours/day, 5 days/week, for 19-74 days (Goldring et al. 1970). Decreased respiratory rate, rhinitis, tracheitis, and bronchopneumonia were observed in 6 rabbits exposed to 70-300 ppm sulfur dioxide for 6 weeks (Miyata et al. 1990). Nasopharyngitis and lipid peroxidation of lung tissue were observed in guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day, for 30 days (Haider 1985).

Significantly increased activities of acid phosphatase and alkaline phosphatase, decreased numbers of epithelial cells, and increased numbers of leukocytes were observed in the bronchial lavage fluid of rats exposed to 30-40 ppm sulfur dioxide for 1 hour/day, 5 days/week, for 12 weeks (Krasnowska et al. 1998). A histopathological evaluation of the bronchial mucosa revealed damage to the epithelium accompanied by infiltration of leukocytes, destruction of cilia, and squamous cell metaplasia, which were more pronounced in rats examined three weeks past exposure compared to those examined immediately after exposure.

Exposure of 12 rats to 400 ppm sulfur dioxide for 3 hours/day, 5 days/week, for up to 42 days resulted in airway effects similar to those observed in humans with chronic bronchitis (Lamb and Reid 1968). A loss of cilia, epithelial necrosis, and a reduction in goblet cell numbers were observed during the first 2-4 days of exposure. By 3-6 weeks of exposure, signs of healing were evident and included a thickened epithelium and the reappearance of shortened cilia. During the same time period, goblet cells increased in size and number and appeared in distal airways, areas in which they are normally lacking. The sialidase-sensitive mucous in distal airways was replaced by sialidase-resistant mucous within three weeks of exposure. Tracheal gland size continually increased throughout the exposure period. Similar effects were observed in another study in which rats were exposed to 400 ppm sulfur dioxide for 3 hours/day, 5 days/week, for up to 3 weeks (Basbaum et al. 1990). An 8-9 fold increase in mucin mRNA transcripts was also observed.

The respiratory toxicity of sulfur dioxide following chronic-duration inhalation exposure has been studied in animals” No effects on lung function were observed in 50 guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972). Likewise, no lung function changes or histopathological alterations in the lung were observed in 9 monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975).

In summary, the available data indicate that sensitive asthmatics may respond to concentrations of sulfur dioxides as low as 0.1 ppm. Healthy nonasthmatics respond to higher concentrations of sulfur dioxide (≥1.0 ppm). Factors that can exacerbate the respiratory effects of sulfur dioxide include exercise and breathing of dry or cold air. Animal data support the human data on respiratory effects of sulfur dioxide.

Cardiovascular Effects. Human, nonasthmatic subjects (n=≤14) exposed to 1-8 ppm sulfur dioxide showed increased pulse rate (Amdur et al. 1953).

No evidence of histological lesions in the heart was found in 9 monkeys following exposure to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no microscopic lesions were detected in the hearts of 50 guinea pigs that were exposed by inhalation to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972). Increased lipid peroxidation was observed in hearts of 6 guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day, for 30 days (Haider 1985). The biological significance of the result is unknown.

Gastrointestinal Effects. Nausea and vomiting were observed in 3 humans exposed to >40 ppm sulfur dioxide during an accident at a copper mine (Rabinovitch et al. 1989).

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to sulfur dioxide.

Hematological Effects. Blood samples were taken from PO0 workers exposed to sulfur dioxide for a minimum of 2 years in a refrigerant manufacturing plant (Kehoe et al. 1932). Prior to 1927, the sulfur dioxide concentration averaged between 80-100 ppm. After the installation of a ventilation system, sulfur dioxide levels typically ranged between 5-35 ppm with occasional peaks as high as 50-70 ppm. Small but significant differences in the numbers of polymorphonuclear leukocytes and lymphocytes were observed. The authors questioned the biological significance of the hematological findings and concluded that it was probably due to the high rate of respiratory infection in both exposure and control groups.

An increase in blood levels of methemoglobin was observed in 45-59 workers in a broom manufacturing factory who were exposed to average sulfur dioxide concentrations of 0.29 and 57.0 ppm in the summer and winter, respectively (Savic et al. 1987). The mean percentage of methemoglobin was elevated during the winter when windows were closed and sulfur dioxide levels were highest. With the exception of dust, exposure to other workplace chemicals was not described.

Numerous studies in animals have demonstrated oxidative effects on erythrocytes. An increase in erythrocyte deformability was observed in 14 rats exposed to 1 ppm sulfur dioxide for 24 hours (Baskurt et al. 1990). Osmotic hemolysis and sulfhemoglobin levels were increased in erythrocytes of 50 rats exposed to 0.9 ppm sulfur dioxide for 24 hours (Baskurt et al. 1988). An increase in the erythrocyte deformability index and lipid peroxidation were noted in the erythrocytes of 12 guinea pigs exposed to 10 ppm sulfur dioxide for 30 days (Dikmenoglu et al. 1991). Significantly increased ratios of methemoglobin and sulfhemoglobin, lipid peroxidation, and increased fragility of erythrocytes, were observed in 7 rats exposed to 10 ppm sulfur dioxide for 1 hour/day, for 45 days (Etlik et al. 1997). Significant changes in antioxidant enzyme activities and increased lipid peroxidation were observed in the erythrocytes of 15 rats exposed to 10 ppm sulfur dioxide for 1 hour/day, 7 days/week, for 8 weeks (Gumusht et al. 1998).

Mixed results have been obtained for sulfur dioxide-induced effects on blood cell numbers in animals. No hematological effects were observed in a chronic toxicity study of 9 monkeys exposed to 5.12 ppm sulfur

dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no hematological effects were noted in guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972). However, statistically significant increases in white and red blood cell counts, as well as hematocrit and hemoglobin levels were observed in 7 rats exposed to 10 ppm sulfur dioxide for 1 hour/day for 45 days (Etlik et al. 1997). Increased hematocrit levels were also observed in 50 rats exposed to 0.9 ppm sulfur dioxide for 24 hours (Baskurt et al. 1988).

Animal studies support the finding in humans that sulfur dioxide induces oxidative effects in erythrocytes. However, both human and animal studies are limited. In the occupational studies, levels of sulfur dioxide varied greatly and individual exposure levels were not measured. In addition, confounding factors such as smoking or exposure to other chemicals were not controlled. Because multiple doses were not tested in any of the animal studies, the dose response relationship is unknown. Data from well designed occupational or animal studies are required before the impact of sulfur dioxide exposure on blood can be assessed.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to sulfur dioxide.

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

Information on hepatic effects in animals from inhalation exposure is very limited. In a chronic toxicity study in monkeys, no histological lesions were detected in 9 monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). In contrast, microscopic examination of 50 guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks, showed an increase in the size of hepatocytes accompanied by cytoplasmic vacuolation (Alarie et al. 1972).

Liver triglyceride and esterfied cholesterol levels were increased in 9 rats fed either a standard diet or a high cholesterol diet and exposed to 10 ppm sulfur dioxide for 24 hours/day, 7 days/week, for 15 days (Lovati et al. 1996). However, exposure of 9 diabetic rats to 5 or 10 ppm sulfur dioxide under the same conditions resulted in a significant reduction in liver triglyceride levels. Additional experiments demonstrated that triglyceride levels increased in nondiabetic rats due to a reduction in lipid catabolism. Because insulin regulates the activity of lipases, it appears that a concurrent drop in insulin levels was responsible for the decreased catabolism in the nondiabetic rats. However, in diabetic rats it was postulated that triglyceride

catabolism may have increased to provide an alternate energy source for glucose. Contrary findings were observed in 6 guinea pigs whose liver cholesterol level decreased following exposure to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1985). Liver triglyceride levels were not measured, but total lipid concentrations in livers of exposed animals were unaffected. Additional studies are needed to define the role of sulfur dioxide in the hepatic metabolism of lipids.

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

Information on renal effects in animals from inhalation exposure is very limited. No renal effects were observed in a chronic toxicity study of 9 monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no renal effects were noted in 50 guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972).

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

Significant dose-related decreases in plasma insulin levels were observed in 9 rats exposed to 5 or 10 ppm sulfur dioxide for 24 hours/day, 7 days/week, for 15 days, but significant effects on insulin levels were not noted in diabetic rats exposed to sulfur dioxide under the same conditions (Lovati et al 1996).

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to sulfur dioxide. Skin irritation was observed in 6 rats and 12 guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1982, 1985).

Ocular Effects. In a case report of a paper mill accident in which five persons were exposed to high concentrations (not specified) of sulfur dioxide for less than 5 minutes, reversible conjunctivitis and superficial cornea1 burns were noted (Charan et al. 1979). In another case report dealing with a pyrite dust explosion that resulted in nine persons being exposed to high levels of sulfur dioxide, conjunctival irritation and cornea1 erosion were observed (Harkonen et al. 1983). The concentration of sulfur dioxide was not measured, but based on experimental explosions, the concentration was estimated to be 30-1,600 ppm. Burning of the eyes was reported in a case study of an accident at a copper mine in which 3 miners were exposed to >40 ppm sulfur dioxide (Rabinovitch et al. 1989). Irritation and tearing were reported by 65% of

workers in a Yugoslavian broom manufacturing plant who were exposed to sulfur dioxide levels averaging between 0.29 ppm in summer and 57 ppm in winter (Savic et al. 1987).

Eye irritation was observed in 6 rats and 12 guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1982,1985).

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

Following 5 weeks of exposure to 70-300 ppm sulfur dioxide, body weight gains of the 6 treated rabbits were 25% lower than those of controls (Miyata et al. 1990). No body weight effects were observed in a chronic toxicity study of 9 monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no body weight effects were noted in 50 guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972) or in 15 rats exposed to 10 ppm sulfur dioxide for 1 hour/day, 7 days/week, for 8 weeks (Gumuslu et al. 1998).

2.2.1.3 Immunological and Lymphoreticular Effects

In a study of 10 mild asthmatic subjects, prior inhalation of 0.2 ppm sulfur dioxide for 6 hours did not significantly affect the provocation dose of *Dermatophagoides pteronyssinus* allergen required to produce a 20% decrease in forced expiratory volume in 1 second (Devalia et al. 1994). However, prior inhalation exposure to a combination of 200 ppb sulfur dioxide and 400 ppb nitrogen dioxide significantly reduced the provocation dose of allergen required to cause a 20% decrease in forced expiratory volume in 1 second.

Increased prevalence of allergies was observed in 556 children (aged 7-13 years) living near an aluminum smelter in Norway for seven years or more (Soyseth et al. 1996). Prevalence was highest in children who lived in the area between the ages of 19-36 months and were exposed to sulfur dioxide levels of 20-24 $\mu g/m^3$ (0.008-0.009 ppm). However, there was no evidence of a dose response relationship. Fluoride levels were also increased in the area, but other air pollutants were not discussed. The data was controlled for age, sex, and in utero exposure to cigarette smoke. However, there was no control for possible confounders such as fluoride or other air pollutants.

The incidence of acute respiratory disease was compared in groups of 2,705-8,991 children (aged 1-1,2 years) living in high and low pollution areas (based on 1973 national primary standards) within four regions of the United States (French et al. 1973). All polluted areas had high concentrations of sulfur dioxide ranging from 63-275 μg/m^3 (0.024-0. 1 ppm). Contaminants which were also present in high concentrations in polluted areas included sulfates in the Salt Eake Basin, metals in the Rocky Mountain communities, and total suspended particulates (TSPs) in New York and Chicago. Generally, increases in incidence of respiratory infection were observed in children who lived in polluted areas for a minimum of 3 years. In the Salt Lake Basin and Rocky Mountain region, effects were greatest in children 4 years-old and younger. However, in Chicago, there was no association between respiratory illness and air pollution in children who were too young to attend nursery school. The discrepancy in results may have resulted from differences in the pollution mixtures or from inadeqluate control of confounding factors.

Increased sensitization to antigen was reported in a study of guinea pigs exposed by inhalation to sulfur dioxide (Riedel et al. 1992). In this experiment, groups of six guinea pigs were exposed to either clean air or 5 ppm sulfur dioxide for 8 hours/day for 5 days, with intermittent inhalation of ovalbumin (8 mg aerosolized) in order to sensitize the animals. Control animals were also sensitized with ovalbumin. Antibodies against ovalbumin were measured before and after sham and sulfur dioxide exposures. Animals were exposed to the ovalbumin for 45 minutes following sham or sulfur dioxide exposure on days 3,4, and 5. Seven days after the last exposure, the guinea pigs were tested for bronchial sensitization to ovalbumin. Sulfur dioxide-treated animals were found to be sensitized to ovalbumin, while pretreatment with anti-inflammatory drugs (methyl-prednisolone, indomethacin, or nedocromilsodium) for 6 days beginning 12 hours before the first sulfur dioxide exposure prevented ovalbumin sensitization.

In an acute-duration inhalation study with hamsters (≤12/group), there was a significant reduction in endocytosis by pulmonary macrophage (process used in defending lung against pathogens and foreign bodies) following exposure to 50 ppm sulfur dioxide for 4 hours while exercising (Skornik and Brain 1990). However, exposure of rats and mice to 0.32-0.43 ppm sulfur dioxide together with 87-113 μg/m^3 sulfate for 4 hours prior to or 17 hours following infection with *StaphyZococcus* aureus or Group C *Streptococci* had no effect on clearance or phagocytosis of *S. aureus* or rates of *Streptococcal* killing and proliferation (Goldstein et al. 1979).

2.2.1.4 Neurological Effects

Reflexes were examined in 100 workers exposed to sulfur dioxide in a refrigerant manufacturing facility for a minimum of 2 years (Kehoe et al. 1932). Prior to 1927, the sulfur dioxide concentration averaged between 80-100 ppm. After the installation of a ventilation system, sulfur dioxide levels typically ranged between 5-35 ppm with occasional peaks as high as 50-70 ppm. A significant number of workers had reflex response times that were slower or faster than normal The authors stated that the effect did not indicate neurological injury but reflected differences in irritability. Neurological effects of sulfur dioxide exposure have been described as psychological responses to general toxicity (Parmeggiani 1983). The Kehoe et al. (1932) study is limited because occupational exposure to other chemicals was not well characterized.

Seizures and prostration were observed in groups of 8 rats prior to death, which occurred following exposure to 2,350,50,000 and 500,000 ppm sulfur dioxide for an average of 176 minutes, <10 minutes, and <2 minutes respectively (Cohen 1973). Transient changes in the frequency of certain behavioral patterns, such as grooming and digging, were noted in 10 male and 10 female mice continuously exposed to 30 ppm sulfur dioxide and observed during the first 9 days prior to mating in a reproductive study (Petruzzi et al. 1996). There was no evidence of neurological effects in the offspring of the mice.

Increased lipid peroxidation was observed in the brains of 6 guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider et al. 1982). However, the study is limited due to small sample size and administration of only one dose. In addition similar studies are not available and the reproducibility of results cannot be verified. Therefore, the biological significance of the results is not known.

2.2.1.5 Reproductive Effects

In a cross-sectional study of spontaneous abortions in an industrial community in Finland, no evidence was found that exposure to sulfur dioxide was associated with a risk of spontaneous abortions (Hemminki and Niemi 1982). Types of industries in the area included pulp paper, metal, viscose rayon, and chemical. Hydrogen sulfide and carbon disulfide were industry-related pollutants which were also present in the area. High sulfur dioxide levels in air were associated with abnormal sperm morphology and decreased motility in 325 18-year-old males in the Czech Republic (Selevan et al. 1995). Because sulfur dioxide was used as a surrogate for all air pollutants, it cannot be determined which chemical or mixture of chemicals was responsible for the effect on sperm.

Reproductive effects, as measured by completed pregnancies, litter size, sex ratio, and neonatal mortality, were not observed in 10 male and 10 female mice continuously exposed to 5, 12, or 30 ppm sulfur dioxide for 9 days prior to mating until days 12-14 of pregnancy (Petruzzi et al. 1996). Pregnancy rate and the number of implants, resorptions, and live fetuses were not affected in 32 mice exposed to 25 ppm sulfur dioxide for 7 hours/day on gestation days 6-16 or in 20 rabbits exposed to 70 ppm sulfur dioxide for 7 hours/day on gestation days 6-18 (Murray et al. 1979). The offspring were not assessed for reproductive function in these studies.

2.2.1.6 Developmental Effects

An association between exposure to increased levels of air pollution during pregnancy and a reduction in birth weight has been reported in humans (Wang et al. 1997) Decreased birth weights were noted for exposure to both sulfur dioxide and TSPs. However, evaluation of these results is complicated by limitations such as confounding effects of various air pollutants and a lack of personal exposure data. Therefore, differentiation of potential developmental effects associated with individual pollutants of a mixture is not possible.

No developmental effects were observed in a study in which 13 pregnant mice were exposed to 32-250 ppm sulfur dioxide on gestation days 7-17 (Singh 1982). Neurological effects, measured by reflexes and learning ability, were not observed in the offspring of 10 mice continuously exposed to 5-30 ppm sulfur dioxide 9 days prior to mating through gestation days 12-14 (Petruzzi et al. 1996). Although there were some transient behavioral effects in dams, there were no signs of systemic maternal toxicity. In another developmental study in mice in which pregnant females were exposed to 32 ppm or 65 ppm on gestation days 7-18, increased time for righting reflex on postnatal day 1 and increased negative geotaxis on postnatal day 10 were reported in offspring (Singh 1989). The duration of exposure for each day was not stated. No visible signs of maternal toxicity and no effect on the number of live births were observed. Sulfur dioxide at a concentration of 65 ppm significantly decreased the birth weight (about 89% of controls) of the pups. Reduced body weight and delayed ossification in sternebrae and occipital bones were observed in the offspring of 32 mice exposed to 25 ppm sulfur dioxide for 7 hours/day on gestation days 6-15 (Murray et al. 1979). Increased numbers of skeletal variations, such as non-ossified sections of frontal bones, fusion of occipital and parietal bones, and extra ribs, were also observed in the offspring of 20 rabbits exposed to 70 ppm sulfur dioxide for 7 hours/day on gestation days 6-l 8 (Murray et al. 1979). Decreased food intake was the only sign of maternal toxicity in mice and rabbits.

2.2.1.7 Genotoxic Effects

Assays of clastogenic effects in humans following occupational exposure to sulfur dioxide via inhalation show mostly positive results. Increases in chromosome aberrations and sister chromatid exchanges were detected in lymphocytes from 42 workers at an Indian fertilizer plant who were exposed to an average concentration of 41.7 mg/m^3 (15.92 ppm) of sulfur dioxide (Yadav and Kaushik 1996). Similar findings were observed in another study of 40 workers exposed to sulfur dioxide in a Chinese sulfuric acid factory (Meng and Zhang 1990a). Exposure concentrations ranged from 0.34 to 11.97 mg/m^3 (0.13 to 4.57 ppm). In addition, increases in the frequencies of lymphocytes with micronuclei were noted (Meng and Zhang 1990b). Confounding exposures were not discussed in these studies" A significant increase in the frequency of chromosomal aberrations was found among 19 workers at a sulfite pulp factory (Nordenson et al. 1980). Exposure concentrations were not reported and workers were also exposed to chlorine and dust. One study of potential chromosomal abnormalities in workers exposed to sulfur dioxide while working in the aluminum industry revealed that sulfur dioxide did not cause an effect (Sorsa et al. 1982).

No studies were located regarding genotoxic effects in animals after inhalation exposure to sulfur dioxide.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

There is no definitive evidence for an increased cancer potential from sulfur dioxide in humans. Several epidemiological studies have been conducted on copper smelter workers and pulp and paper workers who can be exposed to sulfur dioxide (IARC 1992). However, the studies conducted in copper smelters focused primarily on the association between arsenic exposure and cancer. It has also been difficult to separate the potential effects of sulfur dioxide and arsenic exposures in the studies of copper smelter workers. Studies of the potential carcinogenicity of sulfur dioxide are discussed in the following paragraphs.

A cohort study of 5,403 male copper smelter workers showed that respiratory cancer risks in workers exposed to sulfur dioxide for 212 months were not significantly increased when controls for exposure to arsenic were in place (Lubin et al. 1981). The concentration of sulfur dioxide was not specified in the study. In a follow-up mortality study in the same cohort of smelter workers, a clear dose-response relationship between arsenic exposure and respiratory cancer was demonstrated (Welch et al. 1982). Although an

apparent relationship of mortality to sulfur dioxide exposure was observed, workers in the medium and high sulfur dioxide exposure categories had higher exposures to arsenic than those in the low sulfur dioxide exposure groups. The concentrations of sulfur dioxide associated with each exposure category were not specified. The studies by Lubin et al. (1981) and Welch et al. (1982) are limited because exposures to sulfur dioxide and arsenic could not be completely separated.

The results of a case-cohort study of mortality in workers from eight copper smelters in the United States revealed that arsenic was the primary cause of lung cancer in copper smelter workers after adjusting for cigarette smoking and sulfur dioxide exposure (Enterline et al. 1987).

A nested case-control study of lung cancer among 308 workers in a large chemical facility revealed significantly elevated risks for workers with moderate and high potential exposure (≥1 year) to sulfur dioxide (Bond et al. 1986). For workers who had been exposed to sulfur dioxide, the odds ratio for lung cancer was 1.40. Application of multivariate analyses showed a significant trend ($p=0.003$) of increasing lung cancer risk associated with increasing intensity of sulfur dioxide exposure for the comparison with the decedent controls. The odds ratios for lung cancer were 0.48 for low exposure, 1.69 for moderate exposure, and 1.45 for high exposure. No trend was apparent for the comparison with the living controls. Also, the risk of lung cancer did not increase with duration of exposure to sulfur dioxide. Confounding effects from exposure to numerous chemicals was also possible. Products manufactured at the facility included chlorinated solvents, plastics, chlorine, caustic soda, ethylene, styrene, epoxy, latex, magnesium metal, chlornitrogen products, and glycols. Employees were exposed to an average of 7.5 chemicals during their career, and the most common exposures included chlorine, sulfur dioxide, hydrogen chloride, and carbon tetrachloride. The study authors indicated that the findings must be interpreted with caution because such findings have not been reported among other workers with similar exposures.

The relationship between ambient air pollution (including sulfur dioxide) and lung cancer has been examined. Lung cancer cases (2,439 males, 765 females) were identified in Helsinki, Finland, and standardized incidence ratios were calculated for 33 subareas of Helsinski for 1975-1978, 1979-1982, and 1983-1986 (Ponka et al. 1993). Mean annual concentrations of sulfur dioxide were 0.005-0.008 ppm. After adjustment for age, sex, and level of education, the lung cancer risk increased slightly, but nonsignificantly, with increasing sulfur dioxide concentration. Lung cancer was 1.3% higher in the subareas with the highest sulfur dioxide concentrations (≥ 0.008 ppm) compared with the subareas with the lowest concentrations (<.005 ppm). There was no consistent relationship between the concentration of nitrogen dioxide and the

incidence of lung cancer. The study authors concluded that sulfur dioxide had little, if any, effect on the risk of lung cancer.

A retrospective cohort study employing a Poisson regression model for time trends of mortality to detect subtle effects of air pollution on lung cancer mortality in Japan was conducted (Tango 1994). The trend of mortality in females, aged 40-79, was examined in 23 wards of the Tokyo metropolitan area. The size of the cohort was not specified. The ward-specific time trend of nitrogen dioxide and sulfur dioxide concentrations for the years 1972 through 1988 was estimated. The result of this study showed a statistically significant (p=0.0055) association between exposure to nitrogen dioxide and an increased trend of lung cancer mortality. The association for sulfur dioxide exposure was nonsignificant (p=0.0655).

One chronic-duration animal study investigated the potential carcinogenicity of inhaled sulfur dioxide in mice (Peacock and Spence 1967). An experimental group of 35 male and 30 female mice was exposed to 500 ppm sulfur dioxide for 5 minutes/day, 5 days/week, for 2 years. The control group consisted of 41 males and 39 females. Female mice exposed to sulfur dioxide exhibited a significant increase in the incidence of lung tumors (13/30 adenomas and carcinomas versus 5130 in controls; 4/30 primary carcinomas versus none in the controls). The incidence of lung adenomas and carcinomas was also higher in the treated males (15/28 versus 11/35 in controls), but the increase was not significant. The incidence of primary carcinomas in treated males was similar to that of the controls. These data provide limited evidence for the carcinogenicity of sulfur dioxide in the mice. However, the determination of carcinogenic potential is complicated by study limitations. A dose-response relationship could not be assessed because multiple doses were not tested. Due to the small group sizes, it cannot be concluded that increased tumor incidences did not result from chance alone. Quality studies in additional species are reqluired before the carcinogenicity status of the compound can be determined.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans or animals after oral exposure to sulfur dioxide.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or other systemic effects after oral exposure to sulfur dioxide.

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

2.2.2.3 Immunological and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to sulfur dioxide.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to sulfur dioxide.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight, or other systemic effects in humans or animals after dermal exposure to sulfur dioxide.

Dermal Effects. Sulfur dioxide is a severe irritant to the skin (Department of Labor 1975). Sulfur dioxide is a liquid under pressure at 0°C. On the skin, the liquid produces burns from the freezing effect of rapid evaporation (Department of Labor 1975).

No studies were located regarding dermal effects in animals after dermal exposure to sulfur dioxide.

Ocular Effects. Sulfur dioxide is a severe irritant to the eyes (Department of Labor 1975). The eye irritation level is 10 ppm. Exposure of the eyes to liquid sulfur dioxide from pressurized containers can cause cornea1 burns and opacification, resulting in loss of vision It has been reported that ocular damage from exposure to liquid sulfur dioxide is not due to freezing but is characteristic of chemical burns (Grant 1974). Sulfurous acid, which is formed when sulfur dioxide contacts moist surfaces, appears to be the primary cause of eye injury.

Application of pure sulfur dioxide gas (room temperature and atmospheric pressure) directly to the eyes of rabbits for 5 seconds has produced severe damage to the cornea and conjunctiva, similar to effects observed with acid burns (Grant 1974). Opacity of corneas was noted immediately after and 6 months following exposure.

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

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to sulfur dioxide.

2. 3 TOXICOKINETICS

Sulfur dioxide, a highly water-soluble gas, is rapidly absorbed by the mucosa of the nose and upper respiratory tract. Absorption in the lower respiratory tract is increased with enhanced ventilation associated with a transition from nasal to oronasal breathing. Upon contact with moist mucous membranes, sulfur dioxide is hydrolyzed to sulfites which are taken up by the blood and readily distributed throughout the body. Sulfites can either be oxidized to sulfates by sulfite oxidase, primarily in the liver, or they can react with proteins to form S-sulfonate. Sulfates are excreted in the urine.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Studies in humans have shown that sulfur dioxide, a highly water-soluble gas, is rapidly absorbed by the mucosa of the nose and upper respiratory tract (Kleinman 1984; Speizer and Frank 1966). Absorption of sulfur dioxide in the upper respiratory tract is more efficient during nose breathing than during mouth breathing (WHO 1979). Absorption of sulfur dioxide by the mucosa of the lower respiratory tract is minimal because of minimal delivery to this region, but is increased with increased ventilation associated with a transition from nasal to oronasal breathing at a mean minute ventilation of 30 L/mm (EPA 1986d).

Studies in animals indicate that sulfur dioxide is rapidly absorbed by mucosa following inhalation exposure. In rabbits exposed to 100,200, or 300 ppm sulfur dioxide, 90-95% absorption of sulfur dioxide by tissues in the upper respiratory tract was observed (Dalhamn and Strandberg 1961). The rate of absorption of sulfur dioxide by tissues in the nasal cavity was found to be higher than that of tissues of the mouth or pharynx (Dalhamn and Strandberg 1961). A subsequent study in rabbits revealed that absorption of sulfur dioxide is dependent on concentration. At high concentrations (≥100 ppm), sulfur dioxide absorption in tissues of the respiratory tract was ≥90%, while at low concentrations (≤0.1 ppm), absorption was approximately 40% (Strandberg 1964). Studies in dogs have supported the findings that sulfur dioxide is readily absorbed by

mucosa in the upper respiratory tract and that the nose is more efficient than the mouth in removing sulfur dioxide (Balchum et al. 1959, 1960a; Frank et al. 1969).

Studies in humans have indicated that 12-15 % of sulfur dioxide absorbed on nasal mucosa is desorbed and exhaled (Speizer and Frank 1966). The remaining sulfur dioxide metabolites are absorbed into the systemic circulation or are delivered to the lower respiratory system by repeated absorption and desorption from mucosa (Frank et al. 1969). Systemic absorption of sulfur dioxide metabolites from tissues of the upper respiratory tract has been demonstrated in animals. In dogs a small segment of trachea was isolated and perfused with radiolabeled sulfur dioxide ($^{35}SO_2$) while the lungs were ventilated with air to prevent entry of the $^{35}S0_2$ (Balchum et al. 1960a). Detection of ^{35}S in lungs, liver, spleen, and kidneys indicated systemic absorption from the tracheal mucosa. It appears that systemic absorption is more efficient from the lower respiratory tract. Blood and organ levels of 35S were compared in dogs following oronasal or tracheal exposure to $^{35}SO_2$ (Balchum et al. 1959). Following oronasal exposure, levels of ^{35}S were lower in the blood and several organs including the liver, spleen, and lymph nodes. In most dogs the level of ^{35}S remained steady, thus suggesting a slow continued absorption.

2.3.1.2 Oral Exposure

No studies were located regarding absorption of sulfur dioxide after oral exposure in humans or animals.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption of sulfur dioxide after dermal exposure in humans or animals.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

S-sulfonate (R- S- SO^-_3), which forms from the reaction of the sulfur dioxide metabolite, sulfite, and proteins, was measured in the plasma of human subjects following continuous exposure to 0.3, 1.0, 3.0,4.2, or 6.0 ppm sulfur dioxide in a chamber for periods of up to 120 hours (Gunnison and Palmes 1974). Plasma levels of *S*-sulfonate showed a positive correlation with air concentrations of sulfur dioxide.

The results of studies in dogs indicate that absorbed sulfur dioxide metabolites are taken up by the blood and are readily distributed throughout the body (Balchum et al. 1960a; Frank et al. 1967; Yokoyama et al. 1971). The results of a study in dogs exposed to 22±2 ppm radiolabelled sulfur dioxide (^{35}SO,) for 30-60 minutes showed that the radioactivity levels appeared in blood within 5 minutes of the onset of exposure. It was estimated that from 5% to 18% of the radioactivity administered to dogs was contained in the blood by the end of exposure (Frank et al. 1969). In a subsequent study in dogs designed to further examine the distribution of radioactivity in the blood, blood-radioactivity levels increased progressively when the isolated upper airways were exposed to $^{35}SO_2$ for 30-60 minutes (Yokoyama et al. 1971). Blood-radioactivity levels decreased slightly during a postexposure period that lasted up to 3 hours. The radiolabel was more concentrated in the plasma than in the red blood cells. Also, approximately one-third of the radioactivity in plasma was associated with proteins, especially y-globulins. About two-thirds of the radioactivity associated with the red blood cells was intracellular.

The tissue distribution of radioactivity has been studied in dogs administered $^{35}SO_2$ as a gas to either the intact upper airways or to an isolated segment of the trachea (Balchum et al. 1959, 1960a, 1960b). In dogs that breathed 0.47-148 ppm $^{35}SO_2$, via a tracheal canuula, the radioactivity levels were highest in the trachea and lungs, followed by the hilar lymph nodes, kidneys, and esophagus (Balchum 1960b). A lower concentration of radiolabel was noted in other tissues such as the heart muscle, liver, spleen, striated muscle, brain, ovaries, stomach, pancreas, eye, skin, and submaxillary gland. Experiments in dogs in which $^{35}SO_2$ was inhaled through the nose and mouth at concentrations of 1-141 ppm, showed that a large proportion was deposited in the upper airways (Balchum et al. 1959,1960a). Also, dogs breathing $^{35}SO_2$ through the nose and mouth retained a smaller portion of the radiolabel in the trachea, lungs, hilar lymph nodes, liver, and spleen than those breathing similar concentrations via a tracheostomy (Balchum et al. 1959).

Following oronasal inhalation of radiolabeled sulfur dioxide by dogs, 0.01-0.18% of the ^{35}S dose was measured in ovaries and 0.006-0.1% was measured in testicles (Balchum et al. 1959).

2.3.2.2 Oral Exposure

No studies were located regarding distribution of sulfur dioxide after oral exposure.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of sulfur dioxide after dermal exposure.

2.3.3 Metabolism

Following absorption, inhaled sulfur dioxide dissolves on the walls of the moist airways producing a mixture of sulfite, bisulfite, and hydrogen ions (Gunnison et al. 1987). The formation of sulfite (SO^{32-}), bisulfite (HSO^{3-}), and hydrogen ions occurs in accordance with the equilibria depicted below:

$$\underset{\text{pKa = 1.8 p}K_a\text{ = 7.2}}{SO_2 + H_2O \leftrightarrow \overset{+H}{\underset{-H^+}{H_2SO_3}} \leftrightarrow \overset{+H^+}{\underset{-H^+}{HSO_3^-}} \leftrightarrow SO_3^{2-}}$$

Once formed, sulfite can be oxidized to sulfate, a reaction catalyzed by sulfite oxidase which occurs primarily in the liver (Ellenhorn and Barceloux 1988; Gunnison et al. 1987). Sulfite oxidase is present in mitochondria and has been detected in most tissues (Cabre et al. 1990). High sulfite oxidase activity has been measured in the liver, kidney, and heart, but the brain, spleen, lungs, and testis have been found to have low sulfite oxidase activity. Low pulmonary sulfite oxidase activity may explain the findings of a study in which the distribution of sulfite from inhaled sulfur dioxide was restricted largely to the major airways of the lung (Gunnison et al. 1987).

Experiments utilizing sulfite oxidase-competent rats have demonstrated an absence of sulfite in the plasma of rats following inhalation exposure to sulfur dioxide (Gunnison et al. 1987). Decreased activity of sulfite oxidase in sulfite oxidase-deficient rats results in higher *in vivo* concentrations of sulfite. S-sulfonate is the primary chemical form of absorbed sulfur dioxide in the bloodstream (Sheppard 1988; Yokohama et al. 1971).

Sulfite oxidase activity was found to be lower in the livers of young versus mature rats (Cohen 1974). In one day-old rats, sulfite oxidase activity was approximately 1/10 the level of adult rats. Activity increased as the rats matured and at 32 days of age, the liver sulfite oxidase activity was approximately one half the level of

adult rats. The efficiency of the sulfite oxidation reaction depends primarily on the activity of sulfite oxidase (Gunnison and Palmes 1976). However, detoxification of sulfites is not solely dependent on sulfite oxidase activity. It has been demonstrated that rabbits clear injected sulfites at a faster rate than rhesus monkeys, but that the in vitro activity of sulfite oxidase in the primary metabolizing organs is greater for monkeys than rabbits (Gunnison et al. 1977). The study indicates that metabolism of sulfites is dependent on factors in addition to sulfite oxidase activity.

Sulfites can react and become associated with disulfide bonds of plasma proteins, resulting in the formation of S-sulfonates (Gunnison et al. 1987). Further metabolism and subsequent elimination of S-sulfonates is not known However, it has been postulated that disulfide bonds may reassociate resulting in the release of sulfite (Gumnison and Palmes 1973). Another possibility is that glutathione may react with S-sulfonates to either separate S-sulfonates from proteins or form mixed disulfides and sulfites. It is expected that sulfites produced from such reactions would then be metabolized by sulfite oxidase. Reaction of sulfites with plasma proteins may protect tissues against injury, but may also prolong exposure to very low levels of sulfite (Gunnison and Benton 1971).

There is evidence of age related differences in tbe metabolism of sulfite to sulfate and in the formation of a sulfur trioxide radical intermediate. Levels of sulfur trioxide radicals and sulfite oxidase activity were measured in polymorphonuclear leukocytes (PMN's) obtained from healthy young adults (average age 25), healthy older adults (average age 65), 3 centenarians (≥100 years), and 3 Down's syndrome patients (Constantin et al. 1996). Significantly increased amounts of sulfur trioxide radicals were observed in PMN's from healthy adults who had low sulfite oxidase activity. In centenarians and Down's syndrome patients, generation of the sulfur trioxide radical appeared to be the primary mechanism for detoxification of sulfite, and the sulfur trioxide radical formation was not correlated with the sulfite oxidase activity level.

Sulfur dioxide is excreted primarily in the urine as sulfate (Yokoyama et al. 197 1). Increased levels of sulfates have been detected in the urine of dogs (Yokoyama et al. 1971) and humans (Savic et al. 1987) exposed to sulfur dioxide.

Decreased glutathione levels in the lungs of rats exposed to sulfur dioxide suggest that glutathione may be involved in the detoxification process (Langley-Evans et al. 1996). *In vitro* experiments have demonstrated that sulfites, metabolites of sulfur dioxide, react with reduced glutathione to form *S*-sulfoglutathione in a reaction which is catalyzed by thiol transferase (Kagadel et al. 1986). Conversion of *S*-sulfoglutathione by

γ-glutamyltranspeptidase yields S-sulfocysteinylglycine which is hydrolyzed to S-sulfocysteine by renal peptides. S-sulfoglutathione has been detected in lenses and intestinal mucosa of animals and S-sulfocysteine has been observed in body fluids.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

The excretion of inhaled sulfur dioxide has been studied in dogs. In dogs exposed by inhalation to $^{35}SO_2$, ^{35}S was excreted primarily in the urine as sulfate (Yokoyama et al. 197 1). An average of 84.4% of the urinary radioactivity was in the form of inorganic sulfate, while 92.4% was present as total sulfate (Yokoyama et al. 1971). In dogs exposed to $^{35}SO_2$, the rate of excretion of the radiolabel by the kidney has been shown to be approximately proportional to the level of radiolabel in plasma and whole blood (Frank et al. 1967; Yokoyama et al. 1971).

In humans it is estimated that 12-15% of sulfur dioxide absorbed to mucous membranes is desorbed and exhaled (Speizer and Frank 1966). In an experimental study in which the airways were surgically isolated in anesthetized dogs, ^{35}S was detected in expired gas samples following exposure to 22 ppm $^{35}SO_2$ (Frank et al. 1967). The concentration of $^{35}SO_2$ in the expired gas samples was low, representing 1% of the exposure level. The study authors stated that the lungs were releasing the gas during expiration, presumably from pulmonary capillaries.

2.3.4.2 Oral Exposure

No studies were located regarding the elimination and excretion of sulfur dioxide after oral exposure.

2.3.4.3 Dermal Exposure

No studies were located regarding the elimination and excretion of sulfur dioxide after dermal exposure.

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

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

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A

simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

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

At the current time, PBPK models for sulfur dioxide have not been developed.

2.4 MECHANISMS OF ACTION

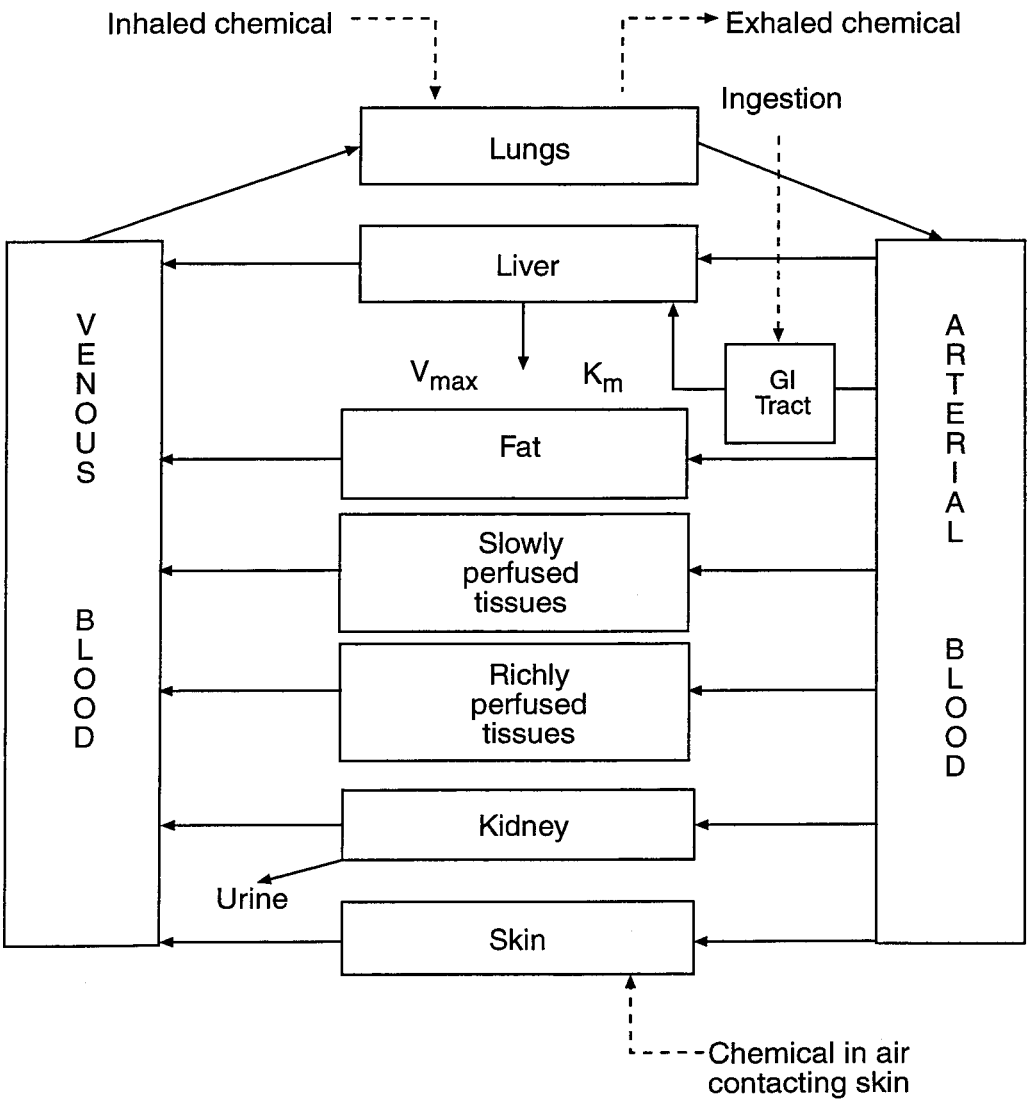
2.4.1 Pharmacokinetic Mechanisms

Sulfur dioxide, a water-soluble gas, is readily absorbed through the upper respiratory tract of both animal species and humans. Once absorbed, sulfur dioxide is mostly metabolized in the liver by sulfite oxidase (Ellenhorn and Barceloux 1988). Sulfites are readily distributed throughout the body. Although significant species-specific differences in sulfite oxidase activity in the liver and kidney have been reported (Tejnorova 1978), potential species-specific differences in the activity of this enzyme in the respiratory tract (the target of sulfur dioxide toxicity in both humans and animals) have not been reported. Sulfur dioxide is excreted in the urine as sulfate.

2.4.2 Mechanisms of Toxicity

Sulfur dioxide-induced increase in airway resistance is due to reflex bronchoconstriction (Frank et al. 1962; Nadel et al. 1965). The reflex nature of bronchoconstriction during inhalation of sulfur dioxide has been demonstrated in humans and in cats (Nadel et al. 1965). Injection of atropine prevented the increase in airway resistance in healthy subjects exposed by inhalation to 4-6 ppm sulfur dioxide for 10 minutes. In another study, atropine increased airway conductance in 11 healthy subjects exposed to 8 ppm sulfur dioxide for 3 minutes but had no effect on 4 asthmatics (Snashall and Baldwin 1982). The finding suggested minimal contribution of cholinergic mechanisms in sulfur dioxide-induced bronchoconstriction in asthmatics. In

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



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

anesthetized, paralyzed, artificially ventilated cats, sulfur dioxide increased pulmonary resistance, an effect prevented by complete cold block of the cervical vagosympathetic nerves or by the injection of atropine.

Studies indicate that sulfur dioxide-induced bronchoconstriction in cats arises from the activation of a muscarinic (cholinergic) reflex via the vagus nerves (Nadel et al. 1965; Sheppard 1988). However, there is some evidence from studies of human asthmatics for the existence of both muscarinic and nonmuscarinic components (Sheppard 1988), with the nonmuscarinic component possibly involving an effect of sulfur dioxide on airway mast cells.

Induction of sulfur dioxide-induced bronchoconstriction by non-cholinergic mechanisms has been demonstrated in humans. The role of prostaglandins in sulfur dioxide-induced bronchoconstriction was investigated by measuring airway responses in asthmatic subjects administered indomethacin, a prostaglandin synthetase inhibitor (Field et al. 1996). A small but significant reduction in airway responsiveness to a sulfur dioxide challenge was noted following administration of indomethacin, thus suggesting a minor role of grostaglandins.

Leukotrienes, which are released by mast cells, may also contribute to sulfur dioxide-induced bronchoconstriction. Administration of zafirlukast, a leukotriene receptor antagonist, to asthmatics resulted in a significant decrease in sulfur-dioxide induced airway responsiveness in 10 out of 12 subjects (Lazarus et al. 1997).

Evidence of noncholinergic mechanisms of sulfur dioxide-induced bronchoconstriction has also been obtained in various animal studies. In guinea pigs partial decreases in response to a sulfur dioxide challenge were noted in 5 out of 7 animals following atropine administration, but results were not significant (Hajj et al. 1996). Results suggested that cholinergic mechanisms may play a minor role in sulfur dioxide responses. However, tachykinins, neuropeptides which are present in the C-fibers of the vagus nerve, were demonstrated to play a larger role in sulfur dioxide-induced bronchoconstriction. Blocking of tachykinin receptors with antagonists, primarily the neurokinin-2 receptor, resulted in a significant attenuation of sulfur dioxideinduced bronchoconstriction in guinea pigs.

Afferent impulses in vagal fibers of the lower respiratory tract were measured in dogs exposed to 200-500 ppm sulfur dioxide for 2 minutes (Roberts et al. 1982). Fifteen out of 34 vagal C-fibers were

stimulated, and the impulses were consistent with sulfur dioxide-induced contraction of tracheal smooth muscle.

It has been postulated that treatment of neonatal rats with capsaicin to eliminate tachykinins through the destruction of C-fibers would result in an attenuation of sulfur dioxide-induced respiratory effects. Responses in isolated lungs from capsaicin-treated and control guinea pigs were compared following exposure to 250 ppm sulfur dioxide for 15 minutes (Bannenberg et al. 1994). Capsaicin treatment eliminated the sulfur dioxide-induced release of tachykinins and significantly reduced bronchoconstriction. Minimal bronchoconstriction was present in the lungs of the capsaicin-treated guinea pigs, thus suggesting effects from additional, unknown mediators. However, different results were obtained in intact rats treated with capsaicin shortly after birth (Long et al. 1997). Exposure to sulfur dioxide at 3 months of age resulted in increased bronchonstriction and airway responsiveness in the capsaicin treated rats. Enhanced *in vitro* responses of tracheal rings to cholinergic substances in the capsaicin group supported the theory that sulfur dioxide effects are primarily mediated through cholinergic components. Another possible explanation is that destruction of the C-fibers resulted in the loss of a protective mechanism in which tachykinins alter breathing patterns to prevent the entry of irritants into the lungs.

The ability of tachykinins to alter breathing patterns in response to a respiratory irritant has been demonstrated in rats. Acute exposure of rats to 5% sulfur dioxide through tracheal cannulas was characterized by an immediate reduction in breathing rate (Wang et al. 1996). However, the effect was no longer noted following treatment of the vagal nerves with capsaicin to destroy C-fibers or following a vagotomy.

The involvement of a cholinergic component in the alteration of breathing patterns following exposure to sulfur dioxide has also been demonstrated. Mice (4/group) who breathed various concentrations of sulfur dioxide between 17-298 ppm experienced a rapid reduction in breathing rate at each concentration (Alarie et al. 1973). When the mice were exposed to the same concentrations via a tracheal cannula, the respiratory rate was unaffected. It was therefore concluded that respiratory suppression occurs through the stimulation of cholinergic trigeminal nerve endings in the nasal mucosa.

In conclusion, sulfur dioxide-induced bronchoconstriction and respiratory inhibition appear to be mediated through vagal reflexes by both cholinergic and non-cholinergic mechanisms. Non-cholinergic components include but are not limited to tachykinins, leukotrienes, and prostaglandins. The extent to which cholinergic

or non-cholinergic mechanisms contribute to sulfur dioxide-induced effects is not known and may vary between asthmatic and healthy individuals and between animal species.

The chemical mechanism underlying the bronchoconstrictive effect of sulfur dioxide has been examined (Sheppard 1988). Sulfur dioxide can dissolve in water to form bisulfite ion, sulfite ion, and hydrogen ion. Studies on the bronchoconstrictor effects of inhaled sulfur dioxide and acidic and basic sulfite solution suggest that sulfite ion is not likely to mediate sulfur dioxide-induced bronchoconstriction. However, the bisulfite ion, which is present at a ratio of 5:1 (bisulfite:sulfite) at physiologic pH and more chemically reactive than sulfite, might mediate the bronchoconstrictor effect. Bisulfite is a nucleophile that can react with many biomolecules by substitution at electrophilic sites (Sheppard 1988). Such reactions can cause disruption of disulfide bonds It has been postulated that bisulfite formed at the airway surface during inhalation of sulfur dioxide may initiate bronchoconstriction by disrupting disulfide bonds present in tissue proteins (Sheppard 1988). Hydrogen ion production is not considered a likely factor since the concentration of hydrogen ions generated by inhaled sulfur dioxide is regarded to be insufficient to cause bronchoconstriction (Sheppard 1988).

Possible mechanisms for the augmentation of sulfur-dioxide bronchoconstriction by cold, dry air have been suggested (Sheppard et al. 1984). Dry air may contribute to bronchoconstriction through heat loss and subsequent airway cooling. Increased osmolarity from water evaporation in airways is another possible mechanism. Induction of bronchoconstriction through the inhalation of hypertonic aerosols has been demonstrated. It is also likely that drying of the upper airways decreases sulfur dioxide absorption in those areas, thus allowing greater concentrations to reach the lower airways.

Bronchial hyperactivity can develop after a single exposure to a very high concentration of sulfur dioxide (Brooks et al. 1985; Harkonen et al. 1983). Respiratory injury includes epithelial cell injury and destruction, airway mucosal edema and inflammation, and airway smooth muscle bronchospasm. This hyperactivity has been termed reactive airway dysfunction syndrome (RADS) (Brooks 1992; Brooks et al. 1985; Goldstein et al. 1979). Subjects with RADS react positively to methacholine challenge. The bronchial epithelial damage results in nonspecific hyperesponsiveness to a wide range of other irritant stimuli.

Inhalation exposure to sulfur dioxide has been shown to alter mucus secretion in animals (Sheppard 1988). There is some evidence that this effect may be mediated by a vagal reflex (Sheppard 1988). Support for this mechanism has been obtained from a study in dogs which showed that a sulfur dioxide-induced increase in

submucosal gland secretion can be abolished by vagal cooling (Sheppard 1988). The mechanism differs from that of acidic aerosols in which toxicity is dependent on hydrogen ion content (Holma 1985). *In vitro* studies have shown that mucus viscosity increases when its pH is lowered below approximately 7.4. The available literature indicates that mucus of asthmatics has a lower pH and that toxicity of acid aerosols is related to a reduction in the buffering and hydrogen ion absorption capacity of the mucus. There is no evidence which indicates that sulfur dioxide-induced changes in mucous secretion are dependent upon hydrogen ion concentration.

Mechanisms which could contribute to clastogenic effects in human lymphocytes (Meng and Zhang 1990a, 1990b; Nordenson et al. 1980; Yadav and Kaushik 1996) have been discussed (Shapiro et al. 1977). Sulfites, metabolites of sulfur dioxide, can inhibit DNA synthesis and induce chromosomal aberrations in human lymphocytes (Yadav and Kaushik 1996). Bisulfite has been shown to deaminate cytosine in bacteria, a reaction which can lead to mutations by the replacement of Guanine-Cytosine (GC) sites with Adenine-Thymine (AT). Bisulfite can also catalyze the crosslinking of proteins and nucleic acids, such as DNA and histones (proteins to which the DNA is bound). Lastly, numerous free radicals are generated during the oxidation of bisulfite to sulfate, and interaction of the free radicals with nucleic acids is possible. Though many of these mechanisms have been demonstrated *in vitro,* it has yet to be verified that the mechanisms are plausible in humans.

2.4.3 Animal-to-Human Extrapolations

The acute pulmonary effect of sulfur dioxide following inhalation exposure has been consistent in both humans and animals. Dose-related increases in airway resistance have been demonstrated in guinea pigs, dogs, and human subjects. There appears to be a good correlation between the dose-response in guinea pigs and asthmatic subjects; therefore, the guinea pig is considered a good model that is predictive of the response of asthmatics (Amdur et al. 1991).

2.5 RELEVANCE TO PUBLIC HEALTH

Overview

The inhalation route is the primary route of exposure to sulfur dioxide. In the atmosphere, sulfur dioxide occurs with other air pollutants including sulfuric acid, sulfur trioxide, ozone, nitrogen dioxide, and

particulates. Sulfur dioxide can undergo transformation to sulfur trioxide and sulfuric acid. Sulfur dioxide tends to be a problem in urban industrial areas, particularly those where industrial activities utilize the combustion of fuels.

Table 2-2 summarizes the health effects of sulfur dioxide. The results of controlled exposure studies in humans have established that exposure to sulfur dioxide can result in lung function changes indicative of bronchoconstriction. Stimulation of sensory receptors in the airways by irritants and chemicals such as sulfur dioxide produces reflex bronchoconstriction that is mediated primarily via cholinergic pathways. Cool, dry air and exercise also cause bronchoconstriction possibly through increased respiration associated with cooling and drying of the airways (Sheppard et al. 1984). Exercising asthmatics, in particular, are sensitive to the pulmonary effects of sulfur dioxide at concentrations as low as 0.1 ppm (Sheppard et al. 1981). It has been estimated that asthmatics represent a subset of approximately 10 million people, or 4% of the population (EPA 1994a, 1994b). The true prevalence of asthmatics though, may be as high as 7-10% of the population. Responses to sulfur dioxide are variable among asthmatics. It is estimated that exposure to 0.2-0.5 ppm sulfur dioxide during moderate exercise would lead to substantial respiratory effects, in only about l0-20% of mild to moderate asthmatics, but the most sensitive individuals could likely experience incapacitating effects (EPA 1994b). The susceptibility of asthmatics to sulfur dioxide-induced respiratory effects is not clear. Severe asthmatics may actually be less prone to adverse respiratory effects because they are less likely to exercise outdoors and more likely to take medication (EPA 1994b). Healthy nonasthmatic individuals can show lung function changes following inhalation exposure to sulfur dioxide concentrations of ≥1.0 ppm. Sulfur dioxide levels in the most polluted urban industrial areas can exceed 1 ppm. Clinical studies have demonstrated that in adolescents and senior citizens, susceptibility to sulfur dioxide is determined primarily by respiratory health status and not age (Koenig et al. 1982a, 1982b, 1983; Rondinelli et al. 1987).

Most clinical studies in humans have demonstrated statistically significant but subtle effects (i.e., in the normal range) which are not considered pathological. Therefore the effects were classified as minimal according to the ATSDR definition which describes minimal effects as “those that reduce the capacity of an organ or organ system to absorb additional toxic stress but will not necessarily lead to the inability of the organ or organ system to function normally.”

Sulfur dioxide was administered through a mouthpiece in many of the clinical studies. A mouth-only exposure eliminates scrubbing by the nasal mucosa and likely results in the delivery of larger doses to the lower airways. Mouth breathing is common during exercise and in individuals with blocked nasal passages,

Table 2-2. Summary of the Health Effects of Sulfur Dioxide[a]

Concentration (ppm)	Effect
≥0.1	Bronchoconstriction in sensitive exercising asthmatics
0.3–1	Possibly detected by taste or smell
1–2	Lung function changes in healthy nonasthmatic individuals
2	ACGIH recommended TLV-TWA
3	Easily detected odor
5	NIOSH recommended U.S. government STEL
6–12	May cause nasal and throat irritation
10	Upper respiratory irritation, some nosebleeds
20	Definitely irritating to eyes; chronic respiratory symptoms develop at this level; respiratory protection is necessary
50–100	Maximum tolerable exposures for 30–60 minutes
≥100	NIOSH recommended immediate danger to life

[a]Modified from Ellenhorn and Barceloux 1988 and WHO 1979

such as asthmatics. However, one group of investigators demonstrated similar results following oral and oronasal exposure of asthmatics to sulfur dioxide (Bethel et al. 1985; Sheppard et al. 1981). A need has been expressed for additional research in the distribution of inhaled air under various conditions (e.g., rest and exercise) and in healthy versus asthmatic subjects (Sheppard et al. 1981).

Acute studies in animals have supported the human data on pulmonary effects of sulfur dioxide (Amdur 1959; Balchum et al. 1959, 1960b). Guinea pigs, in particular, are considered a suitable animal model (Amdur 1966). The dose-response relationship in guinea pigs correlates well with that observed for exercising asthmatics. Exposure to high concentrations of sulfur dioxide has been shown to result in degenerative changes in the olfactory epithelium in mice (Min et al. 1994), cellular necrosis in the trachea and bronchus of rats (Stratmann et al. 1991), nasal epithelial metaplasia and basal cell hyperplasia in rats (Fowlie et al. 1990), bronchitic lesions in hamsters (Goldring et al. 1970), increased goblet cell numbers in rats (Lamb and Reid 1968) and decreased respiratory rate and bronchopneumonia in rabbits (Miyata et al. 1990).

The association between mortality and/or lung function changes and acute exposures to ambient levels of sulfur dioxide that have been examined in epidemiology studies is not clear. In the atmosphere, sulfur dioxide occurs with other pollutants that may also be associated with similar toxicological effects. It has been difficult to separate the potential effects of sulfur dioxide from those of other pollutants in epidemiological studies.

The 1990 Amendments to the Clean Air Act require that emissions of sulfur dioxide be decreased. In accordance with these Amendments, EPA has reviewed the human health effects data on this chemical and has established National Ambient Air Quality Standards (NAAQS). The annual arithmetic mean NAAQS is 0.03 ppm, while the 24-hour limit is 0.14 ppm.

Minimal Risk Levels for Sulfur Dioxide

Inhalation MRLs

- An MRL of 0.01 ppm has been derived for acute-duration exposure (14 days or less) to sulfur dioxide. This MRL is derived from the study by Sheppard et al. (1981) in which exercising mild asthmatics were exposed to ≥0.1 ppm sulfur dioxide for 10 minutes. The two most sensitive subjects developed slight bronchoconstriction after inhaling 0.1 ppm sulfur dioxide. These two subjects showed doserelated increases in airway resistance after exposure to 0.1-0.5 ppm sulfur dioxide. Significant increases in airway resistance were observed in other asthmatics exposed to ≥0.25 ppm sulfur dioxide

during moderate exercise. Other studies in asthmatics have shown lung function changes at concentrations as low as 0.25 ppm (Bethel et al. 1985; Horstman et al. 1986; Myers et al. 1986a, 1986b). A few studies have not reported respiratory effects in asthmatics at 0.25 ppm (Linn et al. 1983b, 1987,1990).

The dose level of 0.1 ppm sulfur dioxide can be considered a minimal LOAEL. This concentration was divided by an uncertainty factor of 9 (3 for the use of a minimal LOAEL and 3 for human variability) to yield a calculated MRL of 0.01 ppm. The uncertainty factor for human variability addresses varying sensitivity among asthmatics and possible increased sensitivity in children. There is concern of increased sensitivity in young children but there is not sufficient data to confirm it (See Section 2.6).

No intermediate-duration or chronic-duration MRLs were derived because the data are insufficient.

Oral MRLS

No oral MRLs were derived since data were not sufficient, and this is not a clinically relevant route of exposure in humans.

Death. Several case studies of human deaths following acute inhalation exposures to high concentrations of sulfur dioxide have been reported (Atkinson et al. 1993; Charan et al. 1979; Harkonen et al. 1983; Huber and Loving 199 1; Rabinovitch et al. 1989). It is not possible, however, to draw accurate or definitive conclusions from these reports as to the levels of exposure. Effects that were described in these reports included asphyxia, secondary to passive pulmonary and visceral congestion, lungs filled with proteinaceous edema fluid, and irreversible airway obstruction. A concentration of 100 ppm is considered immediately dangerous to life and health (HSDB 1998). Excess mortality among the elderly or the chronically sick has been observed in humans exposed to sulfur dioxide, smoke, and particulate matter during acute air pollution episodes (WHO 1979). The deaths were due primarily to respiratory failure. Associations between daily acute mortality and exposure to ambient levels of sulfur dioxide are difficult to assess because of confounders such as the influence of other air pollutants.

In one limited acute study in the mouse, an acute LC_{50} of 3,000 ppm was reported (Hilado and Machado 1977). For rats (n=8/group) continuously exposed to 590, 925, 2350, 50,000, or 500,000 ppm sulfur dioxide, average times of death were 1866,750, 176, <10 and <2 minutes respectively (Cohen et al. 1973). The numbers of rats (n=8/group) which died within 2 weeks following exposure to 224,593,965, 1,168, or 1,319 ppm sulfur dioxide for 4 hours were 0, 0,3,5, and 8 respectively (Cohen et al. 1973).

There are no reports of fatalities in humans or animals exposed by the oral route or solely by the dermal route.

Systemic Effects

Respiratory Effects. Available data indicate that the respiratory system is the primary target system for sulfur dioxide toxicity following inhalation exposure at low levels (EPA 1994a, 1994b; Sheppard et al. 198 1). Numerous controlled studies in humans have documented that acute-duration inhalation exposure to sulfur dioxide causes constriction of the airways, particularly in asthmatics and other sensitive individuals (Sheppard et al. 1981). Bronchoconstriction has been observed in asthmatics exposed to sulfur dioxide at concentrations as low as 0.1 ppm (Sheppard et al. 1981). Studies have also shown that exercise enhances the responsiveness to sulfur dioxide. Other factors that can exacerbate the respiratory effects of sulfur dioxide include exposure to cold or dry air and other pollutants such as sulfuric acid, nitrogen dioxide, and ozone. Healthy nonasthmatics respond to higher concentrations of sulfur dioxide (i.e., ≥1 .0 ppm) (EPA 1994a, 1994b).

Acute exposures to high concentrations of sulfur dioxide can result in severe and irreversible airway obstruction and in edematous lung tissue (Charan et al. 1979; Harkonen et al. 1983). However, actual concentrations of sulfur dioxide causing these effects have not been reported. Bronchitis has been reported following brief, accidental exposures to 100 ppm sulfur dioxide (Skalpe 1964).

Epidemiological studies on the relationship between sulfur dioxide and respiratory effects are limited because of the difficulties in separating potential effects of sulfur dioxide from those of particulates and other pollutants. Some epidemiological studies of children reveal reversible lung function changes such as decreases in FVC and FEV_1 but no effects on respiratory performance were noted in other studies (Agocs et al. 1997; Buchdahl et al. 1996; Dockery et al. 1982; Dodge et al. 1985; Shy et al. 1973). The effects of particulates cannot be separated from those of sulfur dioxide. Likewise, although lung function changes were reported in several occupational studies in which workers were also exposed to other chemicals such as arsenic (Archer and Gillan 1978; Smith et al. 1977). No significant relationship between pulmonary function and exposure to ≥5 ppm sulfur dioxide was noted in studies of potential lung function changes in copper smelter workers (Lebowitz et al. 1979) and steel plant workers (Lowe et al. 1970). Breathing difficulties and cough were reported by workers in a broom manufacturing facility who were exposed to 0.29-57 ppm sulfur dioxide and also to high concentrations of dust (Savic et al. 1987). Irritation and shortness of breath upon

exertion were reported by workers in a refrigeration unit plant who were exposed to sulfur dioxide levels of 5-100 ppm (Kehoe et al. 1932). Cough, sputum production, and difficulty breathing were reported by pulp mill workers exposed to 2-36 ppm sulfur dioxide (Skalpe 1964).

Studies in experimental animals have indicated pulmonary effects of sulfur dioxide following inhalation exposure. Increased airway resistance and decreased compliance were noted in groups of guinea pigs exposed to 2.6 ppm sulfur dioxide for 1 hour (Amdur 1959). Increased pulmonary flow resistance was noted in guinea pigs exposed to 0.16-835 ppm sulfur dioxide (Amdur 1966). Similar effects were observed in dogs exposed to 1.1-141 ppm sulfur dioxide (Balchum et al. 1959). Acute-duration exposure to high concentrations of sulfur dioxide can result in biochemical, clinical, and histological changes in the respiratory systems of the mouse and rabbit. Degenerative changes in the olfactory epithelium were seen in mice exposed to 20 ppm sulfur dioxide for 120 minutes (Min et al. 1994). Rats exposed to 25 ppm sulfur dioxide for up to 5 days displayed nasal epithelial metaplasia and basal cell hyperplasia (Fowlie et al. 1990).

In an intermediate-duration study, mild bronchitic lesions were seen in hamsters exposed to 650 ppm sulfur dioxide for 19-74 days (Goldring et al. 1970). Inflarmnation of the bronchial mucosa was observed in rats exposed to 3040 ppm sulfur dioxide for 1 hour/day, 5 days/week, for 12 weeks (Krasnowska et al. 1998). Nasopharyngitis and lipid peroxidation of lung tissue were observed in guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1985). Increased numbers of goblet cells were observed in the airways of rats exposed to 400 ppm sulfur dioxide for 3 hours/day, 5 days/week (Basbaum et al. 1990; Lamb and Reid 1968).

The respiratory toxicity of sulfur dioxide following chronic-duration inhalation exposure has been studied in animals. No effects on lung function were observed in guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972). Likewise, no lung function changes or histopathological alterations in the lung were observed in monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975).

Cardiovascular Effects. Human, nonasthmatic subjects exposed by inhalation to 1-8 ppm sulfur dioxide for acute durations showed increased pulse rate (Amdur et al. 1953). No studies were located regarding cardiovascular toxicity after oral or dermal exposure.

No evidence of histological lesions in the heart was found in monkeys following exposure to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no microscopic lesions were detected in the hearts of guinea pigs exposed by inhalation to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972). Lipid peroxidation was observed in the hearts of guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1985).

Gastrointestinal Effects. Nausea and vomiting were observed in humans exposed to >40 ppm sulfur dioxide during an accident at a copper mine (Rabinovitch et al. 1989). No studies were located regarding gastrointestinal effects after oral or dermal exposure. No studies were located regarding gastrointestinal effects in animals.

Hematological Effects. Exposure to sulfur dioxide levels of 5-100 ppm did not appear to affect blood cell numbers of workers in a refrigeration unit plant (Kehoe et al. 1932). Methemoglobin levels were increased in the blood of workers exposed to 0.29-57 ppm sulfur dioxide in a broom manufacturing facility (Savic et al. 1987).

An increase in erythrocyte deformability was observed in rats exposed to 1 ppm sulfur dioxide for 24 hours (Baskurt et al. 1990). Lipid peroxidation has been observed in the erythrocytes of rats exposed to 10 ppm sulfur dioxide for 1 hour/day for 45 days (Etlik et al. 1997) or for 1 hour/day, 7 days/week, for 8 weeks (Gumuslu et al. 1998). Osmotic hemolysis and sulfhemoglobin levels were increased in erythrocytes of rats exposed to 0.9 ppm sulfur dioxide for 24 hours (Baskurt et all 1988). An increase in the erythrocyte deformability index and lipid peroxidation was noted in the erythrocytes of guinea pigs exposed to 10 ppm sulfur dioxide for 30 days (Dikmenoglu et al. 1991). No hematological effects were observed in a chronic toxicity study of monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no hematological effects were noted in guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972). However, statistically significant increases in white and red blood cell counts, as well as hematocrit and hemoglobin levels were observed in rats exposed to 10 ppm sulfur dioxide for 1 hour/day for 45 days (Etlik et al. 1997). Increased hematocrit levels were also observed in rats exposed to 0.9 ppm sulfur dioxide for 24 hours (Baskurt et al. 1988).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after exposure to sulfur dioxide.

Hepatic Effects. No adverse hepatic effects have been reported in humans exposed by inhalation to sulfur dioxide No studies were located regarding hepatic effects in humans or animals after oral or dermal exposure.

Information on hepatic effects in animals following inhalation of sulfur dioxide is very limited. In a chronic toxicity study in monkeys, no histological lesions were detected in monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). In contrast, microscopic examination of guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks showed an increase in the size of hepatocytes accompanied by cytoplasmic vacuolation (Alarie et al. 1972). Liver triglyceride and esterfied cholesterol levels were increased in rats fed either a standard diet or a high cholesterol diet and exposed to 10 ppm sulfur dioxide for 24 hours/day, 7 days/week, for 15 days (Lovati et al. 1996). However, exposure of diabetic rats to 5 or 10 ppm sulfur dioxide under the same conditions resulted in a significant reduction of liver triglyceride levels Liver cholesterol levels decreased in guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1985).

Renal Effects. No adverse renal effects have been reported in humans exposed by inhalation to sulfur dioxide. No studies were located regarding renal effects in humans or animals after oral or dermal exposure.

Information on renal effects in animals following inhalation of sulfur dioxide is very limited. No renal effects were observed in a chronic toxicity study of monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no renal effects were noted in guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972).

Dermal Effects. Liquid sulfur dioxide from pressurized containers is a severe skin irritant in humans (Department of Labor 1975). Skin irritation has been observed in rats and guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1982, 1985).

Ocular Effects. In a case report of an industrial accident in which five persons were exposed by inhalation to high concentrations (not specified) of sulfur dioxide for less than 5 minutes, reversible conjunctivitis and superficial cornea1 burns were noted (Charan et al. 1979). In another case report dealing with a pyrite dust explosion that resulted in nine persons being exposed to high levels of sulfur dioxide, conjunctival irritation and cornea1 erosion were observed (Harkonen et al. 1983). The concentration of sulfur dioxide was not measured, but, in experimental explosions, the concentration was estimated to be 30-1,600 ppm. Burning of

the eyes was reported in a case study of an accident at a copper mine in which miners were exposed to >40 ppm sulfur dioxide (Rabinovitch et al. 1989).

Sulfur dioxide gas is an eye irritant, causing burning and lacrimation (Department of Labor 1975). A concentration of 20 ppm is considered definitely irritating to the eyes (Ellenhom and Barceloux 1988). Direct application of sulfur dioxide gas to the eyes of rabbits has resulted in severe damage to the cornea and conjunctiva, similar to that observed with chemical bums (Grant 1974).

Body Weight Effects- No body weight effects have been reported in humans following exposure to sulfur dioxide.

Following 5 weeks of inhalation exposure to 70-300 ppm sulfur dioxide, body weight gains of treated animals were 25% lower than those of controls (Miyata et al. 1990). No body weight effects were observed in a chronic toxicity study of monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Likewise, no body weight effects were noted in guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972) or in rats exposed to 10 ppm sulfur dioxide for 1 hour/day, 7 days/week for 8 weeks (Gumuslu et al. 1998).

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

Significant dose-related decreases in plasma insulin levels were observed in rats exposed to 5 or 10 ppm sulfur dioxide for 24 hours/day, 7 days/week, for 15 days, but significant effects on insulin levels were not noted in diabetic rats exposed to sulfur dioxide under the same conditions (Lovati et al 1996).

Immunological and Lymphoreticular Effects. One study was located that examined the effect of sulfur dioxide on the airway response of human subjects with mild asthma to inhaled house dust mite allergen (Devalia et al. 1994). Prior inhalation of 0.2 ppm sulfur dioxide for 6 hours did not significantly affect the airway response to inhaled antigen, as measured by the dose of allergen required to produce a 20% decrease in forced expiratory volume in 1 second (PD_{20} FEV_1). However, exposure to both 0.2 ppm sulfur dioxide and 0.4 ppm nitrogen dioxide significantly reduced the PD_{20} FEV_1.

Epidemiological studies have indicated that sulfur dioxide air pollution may increase the prevalence of allergies (Soyseth et al. 1996) and incidence of respiratory infections (French et al. 1973) in children. However, both studies were limited by inadequate control of confounding factors and a lack of personal exposure data.

Sulfites are potent sensitizers, and anaphylaxis can occur from exposure to residues in food (IARC 1992; Sheppard 1988; WHO 1979). Since sulfite-containing foods can off-gas sulfur dioxide, it is possible that some of the effects of sulfite ingestion may be due to inhalation of sulfur dioxide (Sheppard 1988).

Increased sensitization to antigen was reported in a study of guinea pigs exposed by inhalation to sulfur dioxide (Riedel et al. 1992). In this experiment, groups of 6 guinea pigs were exposed to air or 5 ppm sulfur dioxide for 8 hours/day for 5 days, with intermittent inhalation of ovalbumin (8 mg aerosolized) in order to sensitize the animals. The guinea pigs were also given two sensitizing injections of *Canida albicans* prior to sulfur dioxide exposure. Animals were exposed to the ovalbumin for 45 minutes following sham or sulfur dioxide exposure on days 3,4, and 5. Seven days after the last exposure, the guinea pigs were tested for bronchial sensitization to ovalbumin. Antibodies against ovalbumin were measured before and after sham and sulfur dioxide exposures. Sulfur dioxide-treated animals were sensitized to ovalbumin. Pretreatment with anti-inflammatory drugs (methylprednisolone, indomethacin, or nedocromilsodium) for 6 days beginning 12 hours before the first sulfur dioxide exposure prevented the sensitization to ovalbumin. Exposure of guinea pigs to 5 ppm sulfur dioxide for 4 hours/day, 5 days/week, for 6 weeks resulted in increased delayedtype dyspneic symptoms (Kitabatake et al. 1995).

In an acute-duration inhalation study with hamsters, there was a significant reduction in endocytosis by pulmonary macrophage following exposure to 50 ppm sulfur dioxide for 4 hours while exercising (Skornik and Brain 1990). However, pulmonary defense mechanisms were not affected in rats and mice exposed to 0.32-0.43 ppm sulfur dioxide together with 87-113 $\mu g/m^3$ sulfate for 4 hours prior to or 17 hours following infection with *Staphylococcus aureus* or Group C *Streptococci* (Goldstein et al. 1979).

Neurological Effects. Variations in reflex response time were observed in workers of a refrigeration unit plant who were exposed to sulfur dioxide concentrations ranging from 5-100 ppm (Kehoe et al. 1932). The effect was not consistent with neurological injury but may have been a psychological response to general sulfur dioxide toxicity. Seizures and prostration were observed in rats following exposure to 2350, 50,000 and 500,000 ppm sulfur dioxide for an average of 176 minutes, <10 minutes, and <2 minutes respectively

(Cohen 1973). Lipid peroxidation has been observed in the brains of guinea pigs exposed to sulfur dioxide for 1 hour/day for 30 days (Haider et al. 1982). Transient changes in the frequency of certain behavioral patterns, such as grooming and digging, were noted in male and female mice continuously exposed to 30 ppm sulfur dioxide and observed during the first 9 days of a reproductive study. There was no evidence of neurological effects in the offspring of the mice (Petruzzi et al. 1996).

Reproductive Effects. In a cross-sectional study of spontaneous abortions in an industrial community in Finland, no evidence was found that exposure to sulfur dioxide was associated with a risk of spontaneous abortions (Hemminki and Niemi 1982). A study conducted in the Czech Republic found that abnormal sperm morphology was associated with sulfur dioxide, which was used as a surrogate for all air pollutants (Selevan et al. 1995). Reproductive effects, as measured by completed pregnancies, litter size, sex ratio, and neonatal mortality, were not observed in male and female mice continuously exposed to 5, 12, or 30 ppm sulfur dioxide for 9 days prior to mating until days 12-14 of pregnancy (Petruzzi et al. 1996). The offspring were not assessed for reproductive function.

Developmental Effects. An association between exposure to increased levels of air pollution during pregnancy and a reduction in birth weight has been reported in humans (Wang et al. 1997). Decreased birth weights were noted for exposure to both sulfur dioxide and total suspended particulates (TSPs). However evaluation of these results is complicated by limitations such as confounding effects of various air pollutants and a lack of personal exposure data. Therefore, differentiation of potential developmental effects associated with individual pollutants of a mixture is not possible.

No developmental effects were observed in a study in which pregnant mice were exposed to 32-250 ppm sulfur dioxide on gestation days 7-17 (Singh 1982). Neurological effects, measured by reflexes and learning ability, were not observed in the offspring of mice continuously exposed to 5-30 ppm sulfur dioxide 9 days prior to mating through pregnancy days 12-14 (Petruzzi et al. 1996). Although there were some transient behavioral effects in dams, there were no signs of systemic maternal toxicity. In another developmental study in mice in which pregnant females were exposed to 32 ppm or 65 ppm sulfur dioxide on gestation days 7-l 8, increased time for righting reflex on postnatal day 1 and increased negative geotaxis on postnatal day 10 were reported (Singh 1989). The duration of exposure for each day was not stated. No visible signs of maternal toxicity and no effect on the number of live births were observed. Sulfur dioxide at a concentration of 65 ppm significantly decreased the birth weight (about 89% of controls) of the pups. Minor skeletal variations were reported in offspring of mice exposed to 25 ppm sulfur dioxide for 7 hours/day on gestation

days 6-l 5 and rabbits exposed to 70 ppm sulfur dioxide for 7 hours/day on gestation days 6-l 8 (Murray et al. 1979). Fetal body weights were also lower in exposed mice. Reduced food intake was the only sign of maternal toxicity.

Genotoxic Effects. There are some limited data showing clastogenic effects in humans following occupational exposure to sulfur dioxide. Increases in chromosome aberrations and sister chromatid exchanges were detected in lymphocytes from 42 workers of an Indian fertilizer factory who were exposed to au average concentration of 41.7 mg/m^3 (15.92 ppm) of sulfur dioxide (Yadav and Kaushik 1996). Confounding factors were not discussed. Similar findings were observed in another study of 40 workers occupationally exposed to sulfur dioxide at a Chinese sulfuric acid plant (Meng and Zhang 1990a). Exposure concentrations ranged from 0.34 mgm^3 to 11.97 mg/m^3 (0.13-4.57 ppm). In addition, increases in the frequencies of lymphocytes with micronuclei were noted (Meng and Zhang 1990b). A significant increase in the frequency of chromosomal aberrations was found among 19 workers at a sulfite pulp factory (Nordenson et al. 1980). Exposure concentrations were not reported and workers were also exposed to chlorine and dust. One study of potential chromosomal abnormalities in workers exposed to sulfur dioxide in the aluminum industry revealed that sulfur dioxide was witbout effect (Sorsa et al. 1982).

Mutations were not observed in germ cells following in viva exposure of animals to sulfites (metabolites of sulfur dioxide). In a dominant lethal test, mutations were not observed in offspring of male mice treated by peritoneal injection with 300 mg/Kg sodium bisulfite on 38 out of 54 days or 400 mg/kg sodium bisulfite 5 days/week for a total of 20 treatments (Russell and Kelly 1975; Shapiro et al. 1977). A specific-locus test was conducted in the same wild type mice from the 400 mg/kg treatment group, which were mated to females with homozygous marker genes for seven loci (Russell and Kelly 1975). Mutations associated with abnormalities in sperm were not observed in 13,568 offspring which were scored for mutations at seven loci. Table 2-3 summarizes data on genotoxicity of sulfur dioxide *in vivo*.

Table 2-4 summarizes data on the genotoxicity of sulfur dioxide *in vitro*. Chromosomal effects were observed following *in vitro* testing with sulfur dioxide. Lymphocytes from healthy donors were cultured and treated with 100 cc of 5.7 ppm sulfur dioxide, which was bubbled through the culture media (Schneider and Calkins 1970). Twenty percent of the hypotonic smears obtained from treated cells contained abnormalities which were characterized primarily by clumping of chromosomes. Abnormalities were not observed in any of the air-treated controls.

TABLE 2-3 Genotoxicity of Sulfur Dioxide *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Human peripheral lymphocytes	Sister chromatid exchanges and chromosomal aberrations	+	Meng and Zhang 1990a
Human peripheral lymphocytes	Micronuclei	+	Meng and Zhang 1990b
Human peripheral lymphocytes	Chromosomal aberrations	+	Nordenson et al. 1980
Human peripheral lymphocytes	Sister chromatid exchanges and chromosomal aberrations	–	Sorsa et al. 1982
Human peripheral lymphocytes	Sister chromatid exchanges and chromosomal aberrations	+	Yadar and Kaushik 1996
Mice (Dominant-Lethal test)	Gene mutations	–	Russell and Kelly 1975; Shapiro et al. 1977
Mice (Specific-locus test)	Gene mutations	–	Russell and Kelly 1975

– = negative result; + = positive result

TABLE 2-4 Genotoxicity of Sulfur Dioxide *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Eukaryotic organisms:				
Animal:				
Cow Oocytes	Chromosomal Aberration	+		Jagiello et al. 1975
Ewe Oocytes	Chromosomal Aberration	+		Jagiello et al. 1975
Plant:				
Tradescantia paludosa clone O_3 (liquid absorption treatment)	Micronuclei	No data	(+)	Ma et al. 1984
Tradescantia paludosa clone 443O (gaseous exposure)	Micronuclei	No data	(+)	Ma et al. 1973
Fungi: *Saccharomyces cerevisiae*	Gene mutation	+	No data	Guerra et al. 1981

+ = positive result; (+) = weakly positive result

Chromosomes from mouse, cow, and ewe oocytes appeared fuzzy following in vitro exposure to 250 μg/m^3 sodium sulfite and fragmentation and clumping were observed in the ewe and cow oocytes (Jagiello et al. 1975). Meiosis was inhibited in mouse and cow oocytes treated with 150 and 500 μg/m^3 sodium sulfite respectively. However, oocyte meiosis was not inhibited in mice administered 1-5 mg sodium sulfite intravenously, thus supporting the conclusion that in vivo exposure of sulfur dioxide will not result in genotoxic effects of germ cells (Jagiello et al. 1975).

Sulfur dioxide induced micronuclei in eukaryotic plants (Ma et al. 1973, 1984). Sulfur dioxide caused gene mutation in *Saccharomyces cerevisiae* (Guerra et al. 198 1).

The available *in vivo* and *in vitro* data indicate a genotoxic potential for sulfur dioxide. The mechanism of the potential genotoxicity of sulfur dioxide is unknown; however, a metabolite of sulfur dioxide, i.e., sulfite, can cause an inhibition of DNA synthesis and induce chromosomal aberrations in human lymphocytes (Yadav and Kaushik 1996).

Cancer. There are no definitive data in humans or animals that indicate a carcinogenic potential for sulfur dioxide. Several epidemiological studies have been conducted on workers in the copper smelting and pulp and paper industries in which exposure to sulfur dioxide can occur (Enter-line et al. 1987; IARC 1992; Lubin et al. 198 1; Welch et al. 1982). However, many of the copper smelter studies focused primarily on the association between arsenic exposure and respiratory cancer (Enterline et al. 1987; Lubin et al. 198 1; Welch et al. 1982). It has been difficult to separate the potential effects of sulfur dioxide and arsenic exposures in the copper smelter studies. IARC has classified sulfur dioxide as a Group 3 carcinogen, i.e., not classifiable as to its carcinogenicity. EPA has not assigned sulfur dioxide a cancer classification.

One chronic-duration animal study investigated the potential carcinogenicity of inhaled sulfur dioxide in mice (Peacock and Spence 1967). Male and female mice were exposed to 500 ppm sulfur dioxide for 5 minutes/day, 5 days/week, for 2 years. A significant increase in the incidence of lung tumors (13/30 adenomas and carcinomas versus 5/30 in controls; 4/30 primary carcinomas versus none in controls) was observed in the female mice. The incidence of lung adenomas and carcinomas was also higher in the treated males (15/28 versus 11/35 in controls), but the increase was not significant. The incidence of primary carcinomas in treated males was similar to that of the controls. Although limited by small sample size and testing of just one dose, the study suggests that sulfur dioxide may be a carcinogen in mice. Studies in additional species are required before a conclusion can be made about carcinogenic potential.

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at I8 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 4993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Widdowson and Dickerson 1964; Foman et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Foman 1966). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Leeder and Kearns 1997; Komori 1990; Vieira et al. 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depend on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not

developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; West et al. 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Clinical studies were conducted to examine respiratory function in healthy, atopic, or asthmatic adolescents (n=8-9, aged 12-17 years) and 10 healthy male seniors (aged 55-73 years) following a mouth only exposure to a mixture of 1 ppm sulfur dioxide and 1 mg/m^3 sodium chloride aerosol (Koenig et al. 1982a, 1982b, 1983; Rondinelli et al. 1987). Adolescents exercised for 10 minutes of a 40 minute exposure period and the seniors exercised for 10 minutes of a 30 minute exposure period. Statistically significant decreases in forced expiratory volume in 1 second (FEV_1) were observed in asthmatic adolescents (-23%), atopic adolescents (-18%), seniors (-8%), and healthy adolescents (-6%). This study concluded that respiratory health status and not age is the primary factor in determining susceptibility to sulfur dioxide in adolescents and adults because asthmatic adolescents were most sensitive to sulfur dioxide and normal adolescents were least sensitive (Rondinelli et al. 1987). However, the study did not examine susceptibility to sulfur dioxide in younger children and adults, so conclusions about sensitivity in infants and preadolescent children cannot be made. Subjects were exposed to sulfur dioxide in combination with sodium chloride aerosols because sulfur dioxide is found together with one or more droplet aerosols in the atmosphere. In two studies, it was verified that exposure to a mixture of sulfur dioxide and sodium chloride aerosol resulted in effects which did not differ significantly from those obtained from exposure to sulfur dioxide alone (Koenig et al. 1982b, 1982a).

Exposure of 9 atopic adolescents (aged 12-18 years) to 0.1 ppm sulfur dioxide by mouth did not result in statistically significant changes in respiratory function parameters (Koenig et al. 1989). However, there was some evidence that exposure to 0.1 ppm sulfur dioxide may potentiate sulfuric acid-induced respiratory effects. Exposure to 0.068 mg/m^3 sulfuric acid by itself resulted in a nonsignificant, 12% increase in total respiratory resistance. However, a statistically significant, 15% increase in respiratory resistance was observed following exposure to both 0.1 ppm sulfur dioxide and 0.068 mg/m^3 sulfuric acid.

Epidemiological evidence indicates a possible association between sulfur dioxide levels in air and respiratory symptoms in children. In a longitudinal study of children in Arizona, increased prevalence of coughing was noted following exposure to high intermittent levels of sulfur dioxide with a peak 3 hour mean >2.5 mg/m^3 (0.95 ppm) and average levels of particulates (Dodge et al. 1985). In Steubenville, OH, small transient reductions in forced vital capacity (FVC) and forced expiratory volume in 0.75 seconds ($FEV_{0.75}$) were observed in children following acute episodes of air pollution with sulfur dioxide levels ≥0.17 ppm and total suspended particulate levels that exceeded the 1979 standard (Dockery et al. 1982).

In New York seasonal levels of sulfur dioxide, 63-71 $\mu g/m^3$ (0.024-0.027 ppm), and other air pollutants (total suspended particulates (TSPs), suspended sulfates, and nitrogen dioxide) were associated with reduced $FEV_{0.75}$, in children aged 9-13 years but not in children aged 5-8 years (Shy et al. 1973). Three years prior to the study, levels of sulfur dioxide, TSPs, and suspended sulfates were greatly reduced. Sulfur dioxide levels previously ranged between 364-435 $\mu g/m^3$ (0.14-0.17 ppm). It was concluded that persistent respiratory effects in the older children resulted from exposure to high levels of sulfur dioxide, TSPs, and suspended sulfates during the first 5-10 years of life. Effects associated with individual air pollutants were not separated and there was no control for other confounding factors.

There was no association between peak expiratory flow rates (PEFR) and seasonal levels of sulfur dioxide, 11-185 $\mu g/m^3$ (0.004-0.071 ppm), and particulate pollution in relation to 60 asthmatic children (aged 9-14 years) residing in Budapest (Agocs et al. 1997). Air pollutants were evaluated separately and numerous confounding factors were controlled. However, the authors discussed limitations such as medication use by subjects and a lack of personal exposure data.

In London, emergency room visits for acute wheezing episodes in children increased by 12% for each 14 $\mu g/m^3$ (0.005 ppm) increase in sulfur dioxide level (Buchdahl et al. 1996). Effects from other air pollutants (ozone and nitrogen dioxide) were not separated in the evaluation of sulfur dioxide but were controlled for in the evaluation of ozone. The association with wheezing episodes in children was strongest for ozone.

Increased prevalence of allergies was observed in 556 children (aged 7-13 years) living near an aluminum smelter in Norway for 7 years or more (Soyseth et al. 1996). Prevalence was highest in children who were exposed to 20-24 $\mu g/m^3$ (0.008-0.009 ppm) sulfur dioxide between the ages of 19-36 months. However, there was no evidence of a dose response relationship and fluoride levels were also increased in the area.

There was some evidence of increased incidence of respiratory infection in children who lived within four regions of the United States with high levels of sulfur dioxide, 63-275 μg/m^3 (0.024-0.1 ppm) and other air pollutants (French at al. 1973). In the Salt Lake Basin and Rocky Mountain region, the highest incidence of respiratory infection was observed in children 4 years-old and younger. However, in Chicago, there was no association between respiratory illness and air pollution in children who were too young to attend nursery school. Polluted areas of the Salt Lake Basin, Rocky Mountain regions, and Chicago were also characterized by high levels of sulfates, metals, and TSPs, respectively. Differences in the chemical composition of air pollutants or inadequate control of confounding factors are possible reasons for the different findings in very young children.

As previously mentioned, epidemiological studies are limited due to confounding effects of particulates and other air pollutants. It has been reported that particulate sulfates, which form when sulfur oxides are released into the atmosphere, have a greater impact on health than sulfur dioxide (Shy 1977). Sulfate levels as low as 0.009-0.013 mg/m^3 may adversely affect lung function and increase the incidence of acute respiratory disease in children. The exposure levels are similar to those associated with adverse cardiopulmonary effects in adults (0.006-0.010 mg/m^3). Additional research is required to assess the impact of individual air pollutants on children's health.

Asthmatics in general are most susceptible to sulfur dioxide exposure, especially during periods of exercise (EPA 1994a, 1994b). Prevalence of asthma is highest in African Americans, children between the ages of 8 to 11, and urban residents (EPA 1994b). Mortality rates associated with asthma are higher in nonwhite individuals, but the reason is not known (EPA 1994b). Increased susceptibility to sulfur dioxide is therefore expected in asthmatic, minority children living in urban areas.

Following inhalation of radiolabeled sulfur dioxide by dogs, a very small percentage of radiolabel was detected in gonads, 0.01-0.18% in ovaries, and 0.006-0.1% in testicles, but the chemical form of the radiolabel was not known (Balchum et al. 1959). There are no known studies which examine whether sulfur dioxide metabolites can pass the placenta or be excreted into breast milk. Because sulfur dioxide and its metabolites are water soluble, accumulation in maternal tissues and subsequent mobilization during pregnancy or lactation is not likely.

Evidence of reproductive and developmental effects in humans is limited. No association was observed between exposure to sulfur dioxide and spontaneous abortion in 1,792 cases of a cross-sectional study of an

industrial community in Finland (Hemminki and Niemi 1982). In the Czech Republic an association was noted between a high sulfur dioxide level (as a marker for all air pollutants) and an increased incidence of abnormality and reduced motility of sperm in 325 18-year-old males (Selevan et al. 1995). A developmental study conducted in China indicated an association between exposure to sulfur dioxide pollution during pregnancy and decreased infant birth weight in 74,671 women (Wang et al. 1997). However, interpretation of such studies is complicated by limitations such as confounding effects of various air pollutants and a lack of personal exposure data.

Reproductive effects following exposure to sulfur dioxide have not been observed in animals. Exposure of male and female mice (10/sex/group) to 5-30 ppm sulfur dioxide for 9 days prior to mating until days 12-14 of pregnancy had no effect upon completed pregnancies, litter size, sex ratio, and neonatal mortality (Petruzzi et al. 1996). Significant differences in pregnancy rate, implantations, resorptions, or live fetuses were not observed in 20 rabbits exposed to 70 ppm sulfur dioxide on gestation days 6-18 or 32 mice exposed to 25 ppm sulfur dioxide on gestation days 5-15 for 7 hours/day (Murray et al. 1977, 1979).

Serious developmental effects following exposure to sulfur dioxide have only been observed in one study. Increased time for righting reflex on postnatal day 1 and negative geotaxis on postnatal day 10 were observed in the offspring of mice exposed to 32 or 65 ppm sulfur dioxide on gestation days 7-18 (Singh 1989). However, neurological effects were not noted in the offspring of 10 mice exposed to 5-30 ppm sulfur dioxide 9 days prior to mating until days 12-14 of pregnancy (Petruzzi et al. 1996). Exposure of mice (13-17/group) to 32-250 ppm sulfur dioxide on gestation days 7-17 did not result in adverse developmental effects (Singh 1982). Serious malformations were not observed in 20 rabbits exposed to 70 ppm sulfur dioxide on gestation days 6-18 and 32 mice exposed to 25 ppm sulfur dioxide on gestation days 5-15 for 7 hours/day, but minor skeletal variations were noted (Murray et al. 1977, 1979). Effects in rabbits included nonossified sections of bone, fusion of cranial bones, and extra ribs. Delayed ossification and decreased fetal weight were observed in treated mice.

Genotoxic compounds could potentially affect children's health through the induction of mutations in the parental germ cells. *In vitro* experiments have demonstrated a genotoxic effect of sulfur dioxide metabolites on animal germ cells, but adverse effects have not been observed following *in vivo* exposure of animals. Mouse, cow, and ewe oocytes were incubated in cell culture media containing sodium sulfite (Jagiello et. al. 1975). An inhibitory effect on meiosis was noted in the mouse and cow oocytes at 150 and 500 μm^3 sodium sulfite, respectively. At 250 $\mu g/cm^3$ sodium sulfite, the chromosomes of all three species appeared

fuzzy. Fragmentation and clumping were also observed in the chromosomes of ewe and cow oocytes. Genetic disorders can occur in the offspring which develop from oocytes containing fragmented chromosomes. Therefore, the effects of sodium sulfite on oocytes were studied following intravenous administration of l-5 mg sodium sulfite to 6 mice (Jagiello et. al. 1975). In *vivo* administration of sodium sulfite had no effect on the meiotic division of the oocytes.

In a dominant-lethal test, mutations were not observed in the offspring of 10 male mice injected peritoneally with 300 mg/kg sodium bisulfite on 38 out of 54 days or 400 mg/kg sodium bisulfite 5 days/week for a total of 20 treatments (Russell and Kelly 1975; Shapiro et al. 1977). Seven and a half weeks later, the mice (wildtype) from the latter treatment group were mated to females with homozygous marker genes for seven loci (Russell and Kelly 1975). No mutations that may have resulted from an abnormality in sperm were observed in a total of 13,568 offspring which were scored for mutations at the seven loci. The authors estimated the upper limit of genetic risk to humans and concluded that exposure to sulfur dioxide would not likely result in adverse genetic effects in germ cells. Studies which examined effects of *in utero* sulfur dioxide exposure on developing germ cells and possible effects on future generations were not located.

One study has also indicated that maternal nutrition may affect the offspring's susceptibility to sulfur dioxide later in life. Increased evidence of pulmonary injury, measured by protein in bronchoalveolar lavage fluid, was observed in 10 rats exposed to a low protein diet (60 g caisin/kg) *in utero* and 0.29 mg/m^3 (0.11 ppm) sulfur dioxide later in life (Langley-Evans et al. 1997).

Studies which specifically examine metabolism in children were not identified. Upon contact with moisture in airways, sulfur dioxide is converted to a mixture of sulfite, bisulfite, and hydrogen ions (Gunnison et al. 1987). Sulfites are then converted to sulfates by sulfite oxidase. Age-related differences in sulfite oxidase activity have been demonstrated in rats (Cohen 1974). In 1-day-old rats, liver sulfite oxidase activity was approximately 1/10 the level of adult rats. Activity increased as the rats matured and at 32 days of age, the liver sulfite oxidase activity was approximately one half the level of adult rats. Decreased sulfite oxidase activity may result in increased susceptibility to oxidative effects due to increased formation of a sulfur trioxide radical intermediate (Constantin 1996). Animal studies have demonstrated an inverse relationship between sulfite oxidase activity and susceptibility to intraperitoneally administered bisulfite as measured by lethality (Tejnorova 1978).

Pharmacokinetic studies or PBPK models which specifically look at absorption, distribution, and excretion in children or immature animals were not identified. The solubility of gases determine where in the respiratory tract absorption will occur and absorption in the lungs is based upon the blood-to-gas partition coefficient (Amdur et al. 1991). Because solubility and blood-to-gas partition coefficient are constants, absorption of sulfur dioxide in children is expected to be similar to that of adults. Distribution and excretion are also expected to be similar in children and adults. General information about pharmacokinetics can be obtained in Section 2.3.

Studies which determine if mechanisms of toxicity differ in children were not identified. Evidence indicates that sulfur dioxide-induced bronchoconstriction occurs through reflexes which are mediated by cholinergic and noncholinergic factors The percent contribution from cholinergic versus noncholinergic mechanisms is not known and it could potentially differ between children and adults. However, this has not been verified througb research. General mechanisms of toxicity are discussed in Section 2.4.

There are no studies which look at interactions with other chemicals that are unique to children. Studies in animals have indicated that exposure to other air pollutants may potentiate reproductive or developmental effects of sulfur dioxide. Exposure of 20 rabbits to a mixture of 70 ppm sulfur dioxide and 250 ppm carbon monoxide 7 hours/day on gestation days 6-18 resulted in a significant increase in resorptions/litter, which was not observed with exposure to sulfur dioxide or ozone alone (Murray et al. 1977, 1979). Exposure of 32 mice to a combination of 25 ppm sulfur dioxide and 250 ppm carbon monoxide 7 hours/day on gestation days 5-l 5 potentiated the decrease in fetal weight gain which was observed with exposure to sulfur dioxide alone (Murray et al. 1977,1979). Exposure of pregnant mice to ozone alone had the opposite effect and resulted in a significant increase in fetal weight gain. A significant decrease in fetal crown-rump length was also observed in the same mice following exposure of dams to the mixture of pollutants but not sulfur dioxide alone. Effects on fetal crown-rump length following exposure to ozone alone were not discussed.
It is not known whether biomarkers or methods for reducing toxicity to exposure differ in children.
In conclusion, studies of susceptibility in children are limited. Clinical studies have indicated that compared to senior citizens, adolescents are not at increased risk of respiratory effects following inhalation of sulfur dioxide. Adverse respiratory effects may be associated with exposure of children to air pollution, but it is difficult to determine if sulfur dioxide is directly responsible for those effects. The genotoxic potential of sulfur dioxide metabolites has been demonstrated through *in vitro* studies, but *in vivo* exposure of animals

has indicated that mutations in germ cells are unlikely following inhalation exposure of sulfur dioxide. Difficulties in separating the effects of individual air pollutants also complicate the evaluation of sulfur dioxide pollution on human reproduction and gestational development. Results from animal developmental studies are equivocal. Most animal studies have indicated a lack of serious developmental effects but other studies have reported developmental delays which might have resulted from decreased food intake by dams. Lastly, decreased sulfite oxidase activity in young animals has been demonstrated. If the same is true for children, they may be at increased risk for oxidative damage.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAUNRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to sulfur dioxide are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (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., DNA adducts). Biomarkers of effects caused by sulfur dioxide are discussed in Section 27.2.

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 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Sulfur Dioxide

No studies pertaining to specific biomarkers used to identify or quantify exposure to sulfur dioxide were located.

Sulfur dioxide metabolites are rapidly absorbed from the upper respiratory passages and are readily distributed throughout the body (Balchum et al. 1960a; Frank et al. 1967; Kleinman 1984; Speizer and Frank 1966; Yokoyama et al. 197 1). Sulfur dioxide reacts with plasma proteins to form *S*-sulfonates. *S*-Sulfonate levels in human plasma showed a positive correlation with atmospheric levels (> 0.3 ppm) of sulfur dioxide (Gunnison and Palmes 1974). Therefore, plasma S-sulfonate levels may serve as a potential indicator of exposure to sulfur dioxide.

Inhaled sulfur dioxide is excreted in the urine as sulfate. However, sulfur dioxide is not the only source of sulfate in the urine. Sulfates are also metabolites of sulfur-containing amino acids and are therefore normal constituents of intracellular fluids and urine (Vander et al. 1975; Lentner 1981). Concentrations of sulfates in urine range from 53 μmol/dL/Kg in l-day-old infants to 500 μmol/dL/Kg in young men (Lentner 1981). The level of urinary sulfate is a measure of the quantity and quality of proteins in the diet.

2.7.2 Biomarkers Used to Characterize Effects Caused by Sulfur Dioxide

No specific biomarkers used to characterize effects caused by sulfur dioxide were located.

The upper respiratory system is the primary target of sulfur dioxide. Alterations in pulmonary function parameters, such as increased airway resistance, decreased airway conductance, and decreased expiratory volume, might be considered potential biomarkers to characterize effects caused by sulfur dioxide, but alterations in pulmonary function parameters are not specific for sulfur dioxide and may indicate exposure to other air pollutants such as nitrogen dioxide or ozone.

An increase in the number of leukocytes in bronchoalveolar lavage fluid is a biomarker for inflammatory effects of sulfur dioxide exposure (Sandstrom 1989a, 1989b). However, the effect is not specific to sulfur dioxide because inflammation can occur following exposure to numerous irritating substances.

DNA adduct formation in the nasal mucosa is a potential biomarker which could be used in the future. The formation of adducts between the DNA base cytosine and bisulfite, a metabolite of sulfur dioxide, has been demonstrated *in vitro* (Shapiro 1977). Adduct formation in placentas of women from industrial and agricultural areas in the Czech Republic has been compared in order to assess toxicity from exposure to pollution, and no differences were found between the two groups (Topinka et al. 1995). However, the nasal mucosa is the optimal tissue for the development of biomarker techniques because it is the first to contact inhaled toxicants (Flato et al. 1996). A technique for measuring adduct formation in cells obtained from nasal lavage has been demonstrated (Flato et al. 1996). However, studies are needed to verify the formation of bisulfite adducts in nasal mucosa. Adduct formation would not be specific to sulfur dioxide because adducts can form after exposure to numerous carcinogenic and mutagenic compounds.

Clastogenic effects in humans following occupational exposure to sulfur dioxide via the inhalation route have been reported. Increases in chromosome aberrations and sister chromatid exchanges were detected in lymphocytes from 42 workers who were occupationally exposed to an average concentration of 41.7 mg/m^3 (15.92 ppm) of sulfur dioxide (Yadav and Kaushik 1996). Similar findings were observed in another study of 40 workers occupationally exposed to sulfur dioxide (Meng and Zhang 1990a). Exposure concentrations ranged from 0.34 to 11.97 mg/m^3 (0.13 to 4.57 ppm). In addition, increases in the frequencies of lymphocytes with micronuclei were noted (Meng and Zhang 1990b). Such clastogenic effects may serve as potential biomarkers for genotoxic effects of sulfur dioxide. However, these clastogenic effects are not specific for sulfur dioxide and could indicate exposure to other chemicals.

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

2.8 INTERACTIONS WITH OTHER CHEMICALS

Epidemiological studies of the associations between effects of sulfur dioxide and exposure to other chemicals are limited because of the presence of other air pollutants as confounders. A number of other air pollutants such as nitrogen dioxide, sulfuric acid, particulate matter, and ozone can result in respiratory effects similar to those of sulfur dioxide. There is some evidence that particulate matter, which is capable of oxidizing sulfur dioxide to sulfuric acid, can cause a three- to four-fold potentiation of the irritant response in guinea pigs (Amdur 1969). It is postulated that binding of acids to carbon particles may impede neutralization by ammonia in the airways or buffering system in epithelium (Jakab 1996). Under conditions of high relative humidity, sulfate is produced from mixtures of sulfur dioxide and carbon particles. Acute exposure of mice to a mixture of carbon particles and sulfur dioxide at 85% relative humidity resulted in an inhibition of phagocytosis by alveolar macrophages, which was not observed from exposure to sulfur dioxide alone (Jakab 1996).

Concurrent exposures to sulfur dioxide, smoke, and particulates have been associated with symptoms including: increased respiratory effects, increased frequencies of respiratory illness, excess mortality, and worsening of existing respiratory disease (WHO 1979). Table 2-5 summarizes the effects of concurrent exposure to sulfur dioxide, smoke, and particulates, and it designates which portions of the population are affected.

In a controlled study of asthmatic subjects, an enhanced responsiveness to 0.75 ppm sulfur dioxide after exposure to 0.25 ppm nitrogen dioxide for 30 minutes was reported (Jorres and Magnussen 1990). The authors suggested that acute exposure of asthmatics to nitrogen dioxide at rest enhances airway responsiveness to hyperventilation of sulfur dioxide without altering airway tone. In another study of asthmatics, the influence of prior exposure to a low concentration of ozone (0.12 ppm) on the pulmonary response to a subthreshold concentration of sulfur dioxide (0.1 ppm) was examined (Koenig et al. 1990). Prior exposure to ozone potentiated subsequent responses to sulfur dioxide in asthmatic subjects.

The effects of exposure to a combination of sulfur dioxide (0.2 ppm) and nitrogen dioxide (0.4 ppm) on the airway response of mild asthmatic patients to allergen inhalation have been investigated (Devalia et al. 1994). Subjects were exposed for 6 hours to sulfur dioxide and nitrogen dioxide alone, or in combination, in exposure chambers. The subjects were then challenged with predetermined concentrations of Dermato phagoides pteronyssinus allergen 10 minutes after each exposure. The cumulative breath units of allergen

Table 2-5. Symptoms Associated with Concurrent Exposure to Sulfur Dioxide, Smoke, and Particulates[a]

Sulfur Dioxide Concentration (ppm)	Effects
0.01	Increased respiratory symptoms among the general population and increased frequencies of respiratory illness among children
0.04	Excess mortality among the elderly or the chronically sick
0.04	Worsening of the condition of patients with existing respiratory disease

[a]WHO 1979

required to produce a 20% fall in forced expiratory volume in 11 second (PD_{20} FEV_1) were measured after each exposure. The results showed that only the combination of sulfur dioxide and nitrogen dioxide significantly (p=0.005) decreased PD_{20} FEV_1.

Exposure to sulfur dioxide may enhance ozone absorption in the lung. Absorption of ozone boluses were compared in healthy nonsmokers before and after exposure to 0.36 ppm sulfur dioxide for 2 hours (Rigas et al. 1997). Sulfur dioxide exposure resulted in an increased absorption of ozone in males, but the results were not statistically significant. It was postulated that anatotical variations, such as differences in dead space volume, may have contributed to the sex-specific differences in absorption.

Sulfur dioxide (0.1 ppm) by itself had no statistically significant effect on forced expiratory volume in one second (FEV_1) or total respiratory resistance in 9 atopic adolescents (aged 12-18 years) who were exposed by mouth, while exercising for 10 minutes of a 40 minute exposure period (Koenig et al. 1989). However, sulfur dioxide may potentiate sulfuric acid-induced respiratory effects. Exposure to 0.068 mg/m^3 sulfuric acid (0.6 μm aerosol) by itself resulted in a nonsignificant 12% increase in total respiratory resistance. However, a statistically significant 15% increase in respiratory resistance was observed following exposure to both 0.1 ppm sulfur dioxide and 0.068 mg/m^3 sulfuric acid.

A synergistic toxic action between sulfur dioxide and sulfuric acid has been observed in studies of bronchoconstriction in guinea pigs (Amdur 1959, 1974). Particle size of the aerosol was found to be an important factor in the potentiation of the response to sulfur dioxide. For instance, a potentiation of the response to sulfur dioxide was noted when the sulfuric acid particle size was 0.8 microns (μ) but not when the particle size was 2.5 μ.

Sulfite may potentiate effects induced by peroxynitrite, a compound commonly found in lungs of individuals with inflammatory diseases such as asthma (Reist et al. 1998). Peroxynitrite inactivates al-antiproteinase, which inhibits lung damaging enzymes such as elastase. In vitro experiments have demonstrated potentiation by sulfite only if its concentration does not exceed that of peroxynitrite.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to sulfur dioxide than will most persons exposed to the same level of sulfur dioxide in the environment. Reasons may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of sulfur dioxide, or compromised function of target organs affected by sulfur dioxide. Populations who are at greater risk due to their unusually high exposure to sulfur dioxide are discussed in Section 5.7, Populations With Potentially High Exposure.

Exercising asthmatics are recognized as the most susceptible group to sulfur dioxide inhalation (EPA 1994a, 1994b). Some sensitive asthmatics have been shown to respond to sulfur dioxide at a concentration as low as 0.1 ppm (Sheppard et al. 1981). In particular, physically active asthmatics would be at special risk (EPA 1994a, 1994b). In addition, based on data pertaining to the prevalence of asthma and mortality rates from asthma, certain minority group individuals (e.g., African American, Hispanic) may also represent population segments at increased potential risk for sulfur dioxide respiratory effects (EPA 1994a, 1994b) given the higher rates of asthma mortality in nonwhite populations. A sulfite-sensitive subpopulation of asthmatics, who have a relative deficiency of sulfite oxidase, has been postulated to exist (IARC 1992). In contrast, healthy nonasthmatic individuals do not experience respiratory effects at concentrations of up to 1.0 ppm. Nonasthmatic individuals who are unusually sensitive to cold air may also be more susceptible to the respiratory effects of sulfur dioxide.

Elderly adults with preexisting respiratory or cardiovascular disease may be susceptible to the increased risk of mortality associated with acute-duration exposure to sulfur dioxide (WHO 1979). Children may be particularly susceptible to increased frequencies of respiratory illness following chronic-duration exposure to sulfur dioxide (WHO 1979).

Individuals who are deficient in sulfite oxidase may be susceptible to oxidative effects following exposure to sulfur dioxide. *In vitro* studies have demonstrated increased formation of a sulfur trioxide radical intermediate in polymorphonuclear leukocytes of individuals with decreased sulfite oxidase activity (Constantin 1996). Elderly adults and individuals with Down's syndrome may also be susceptible to oxidative stress because limited evidence indicates increased formation of the sulfur trioxide radical regardless of sulfite oxidase activity (Constantin, 1996). Animal studies have demonstrated an inverse relationship between sulfite oxidase activity and susceptibility to intraperitoneally administered bisulfite (Tejnorova 1978).

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to sulfur dioxide. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to sulfur dioxide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. For specific information about treatment following exposures to sulfur dioxide, the reader should consult the text of Bronstein AC and Currance PL (1994): Emergency Care for Hazardous Materials Exposure.

2.10.1 Reducing Peak Absorption Following Exposure

There are no specific methods available to reduce the absorption of sulfur dioxide following exposure. Supportive treatment includes administration of 100% humidified supplemental oxygen with assisted ventilation as required, endotracheal intubation or tracheostomy if upper airway obstruction is present, and the use of inhaled sympathomimetic bronchodilators, such as albuterol, metaproterenol, or cromolyn sodium, for bronchoconstriction (HSDB 1996). For eye contamination, copious irrigation is recommended (HSDB 1998).

2.10.2 Reducing Body Burden

There are no known methods for reducing the body burden of sulfur dioxide. Following absorption, inhaled sulfur dioxide dissolves on the walls of the moist airways to form sulfite and bisulfite, which in turn, can be oxidized to sulfates, a reaction catalyzed by sulfite oxidase (Gunnison et al. 1987). An inverse correlation between sulfite oxidase activity and sensitivity to bisulfite toxicity has been noted (IARC 1992; Tejnorova 1978).

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

Sulfur dioxide-induced increase in airway resistance is due to reflex bronchoconstriction (Frank et al. 1962; Nadel et al. 1965). Injection of atropine prevented the increase in airway resistance in healthy subjects exposed by inhalation to 4-6 ppm sulfur dioxide for 10 minutes. Indomethacin, a prostaglandin synthetase inhibitor, and zafirlukast, a leukotriene receptor antagonist, were demonstrated to reduce airway

responsiveness in asthmatics challenged with sulfur dioxide (Field et al. 1996; Lazarus et al. 1997). Inhaled sympathomimetic bronchodilators can also be used to reverse bronchospasm. Inhaled corticosteroids may be used to alleviate bronchoconstriction associated with reactive airways dysfunction syndrome (RADS) (Kennedy et al. 1992).

Several techniques have been demonstrated to reduce sulfur dioxide-induced toxicity in animals. Administration of low molecular weight heparin to rats during or after exposure to 30-40 ppm sulfur dioxide for 1 hour/day, 5 days/week, for 12 weeks reduced inflammation of the bronchial mucosa (Krasnowska et al. 1998). Treatment with nebulized S-carboxymethylcysteine, a medication prescribed for sinusitis in the United Kingdom and Japan, restored ciliary function and accelerated mucosal repair in the sinuses of rabbits exposed to 20 ppm sulfur dioxide 4 hours/day for 4 weeks (Sugiura et al. 1997).

Administration of vitamins E and C to 7 rats exposed to 10 ppm sulfur dioxide for 1 hour/day for 45 days reduced oxidative effects such as lipid peroxidation and membrane damage in erythrocytes (Etlik et al. 1997).

Once absorbed by the respiratory tract, sulfur dioxide can form sulfite and bisulfite. The enzyme sulfite oxidase can oxidize sulfite and bisulfite to sulfates. Sulfite and/or bisulfite may be the chemicals that play a role in the sulfur dioxide-induced bronchoconstriction (Sheppard 1988). Interference with the formation of sulfite and/or bisulfite may be a potential strategy, albeit untested, to reduce bronchoconstriction from sulfur dioxide toxicity.

2.11 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of sulfur dioxide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of sulfur dioxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that

all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.11.1 Existing Information on Health Effects of Sulfur Dioxide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to sulfur dioxide are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of sulfur dioxide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

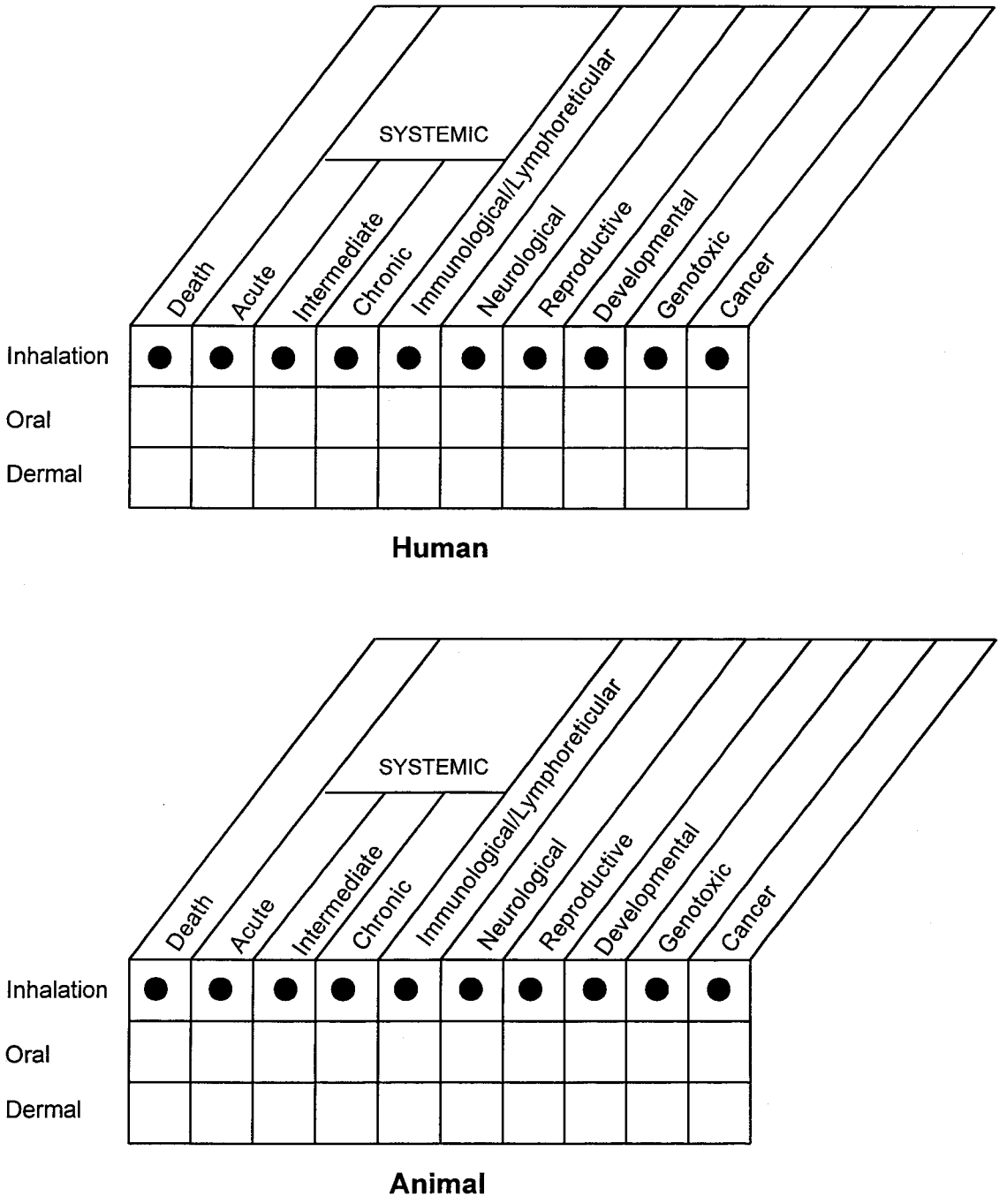
There are human data on inhalation exposure to sulfur dioxide that provide information on acute and chronic systemic effects. There are also limited data on genotoxic and carcinogenic effects. Data on potential chronic systemic, genotoxic, and carcinogenic effects are Bimited because of confounding factors such as multiple exposure. There are no oral or dermal exposure data.

Animal data on inhalation exposure cover primarily acute respiratory effects. Data on other acute-duration effects in animals are limited. There are limited data concerning intermediate- and chronic-duration systemic effects in animals. One chronic study is available that examines potential carcinogenicity of sulfur dioxide in mice. Studies which examine ocular and dermal effects from exposure to the liquid and gaseous form of sulfur dioxide are available. There are no oral exposure data.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. There are several case reports of deaths in humans (Atkinson et al. 1993; Charan et al. 1979; Harkonen et al. 1983; Huber and Loving 199 1; Rabinovitch et al. 1989). However, estimates of exposure concentrations were not often reported in these studies.

FIGURE 2-3. Existing Information on Health Effects of Sulfur Dioxide



There are numerous acute-duration controlled inhalation studies in humans concerning respiratory effects. These studies have established that acute-duration exposure to sulfur dioxide causes constriction of the airways, especially in exercising asthmatics (Bethel et al. 1985; EPA 1994a, 1994b; Horstman et al. 1986; Linn et al. 1983a, 1983b, 1987, 1990; Roger et al. 1985; Sheppard et al. 1980, 1981). Pulmonary function tests in exercising, mild asthmatics indicate that 0.1 ppm sulfur dioxide may be close to the threshold for bronchoconstriction (Sheppard et al. 1981). Based on a minimal LOAEL of 0.1 ppm for increased airway resistance observed in the Sheppard et al. (1981) study, an acute-duration MRL of 0.01 ppm was derived. Studies in experimental animals have supported the pulmonary effects of sulfur dioxide following inhalation exposure. Increased airway resistance and decreased compliance were noted in guinea pigs exposed to 2.6 ppm sulfur dioxide for 1 hour (Amdur 1959).

In recent years, there has been concern about the potential health significance of 5-10 minute exposures to peak levels of sulfur dioxide currently occurring near heavy industrial areas (EPA 1994a, 1994b). Additional studies on the frequency of occurrence of 5-10 minute peak sulfur dioxide levels in the ambient air and the number of asthmatics that may be potentially exposed to such peak levels of sulfur dioxide would be useful in assessing the health effects of exposure to peak levels of sulfur dioxide. In addition, information on the frequency at which asthmatics would be potentially exposed to peak levels of sulfur dioxide would be helpful. Although epidemiological studies on the association between short-term peaks of sulfur dioxide and potential health effects in asthmatics, including exercising asthmatics, would be useful, these kinds of studies are most likely difficult to design and conduct.

The controlled human exposure studies of sulfur dioxide are typically restricted to mild asthmatics. Thus, it is not certain if such studies, although consistent in demonstrating the sensitivity of asthmatics to sulfur dioxide, reflect the characteristics of the asthmatic population as a whole. Individuals with severe asthma may be more susceptible to the effects of sulfur dioxide because of their lower reserve of lung function. However, severe asthmatics may actually be protected against sulfur dioxide effects because they are less prone to strenuous outdoor exercise and more likely to take medication before participating in outdoor activities (EPA 1994b). Additional information on this issue would be useful.

Although oral and dermal data regarding the effects of sulfur dioxide were not identified, human exposure would be expected to be principally by inhalation. Oral and dermal exposure studies may be clinically relevant but are not a high priority.

Intermediate-Duration Exposure. There are no human data on intermediate-duration inhalation exposures to sulfur dioxide. Studies on intermediate-duration exposures to sulfur dioxide would be useful for assessing potential health risks to humans. No intermediate-duration oral or dermal studies of sulfur dioxide were identified. Because inhalation is the primary route of concern, oral and dermal exposure studies should not be a high priority.

Intermediate-duration inhalation exposure studies in animals are very limited. In an intermediate-duration study, mild bronchitic lesions were seen in hamsters exposed to 650 ppm sulfur dioxide for 19-74 days (Goldring et al. 1970). Decreased respiratory rate, rhinitis, tracheitis, and bronchopneumonia were observed in rabbits exposed to 70-300 ppm sulfur dioxide for 6 weeks (Miyata et al. 1990). Inflammation of the bronchial mucosa was observed in rats exposed to 30-40 ppm sulfur dioxide for 1 hour/day, 5 days/weeks, for 12 weeks (Krasnowska et al. 1998). Increased numbers of goblet cells were observed in the airways of rats exposed to 400 ppm sulfur dioxide for 3 hours/day, 5 days/week, for 3 weeks (Basbaum et al. 1990; Lamb and Reid 1968). Nasopharyngitis and lipid peroxidation of lung tissue were observed in guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour/day for 30 days (Haider 1985). Systemic effects have also been noted following inhalation of sulfur dioxide. Lipid peroxidation was observed in erythrocytes of rats exposed to 10 ppm sulfur dioxide for 1 hour/day for 45 days (Etlik et al. 1997) or for 1 hour/day, 7 days/week, for 8 weeks (Gumuslu et al. 1998). A reduction in insulin plasma levels and increase in liver triglyceride levels were observed in rats exposed to 10 ppm sulfur dioxide for 24 hours/day, 7 days/week, for 15 days (Lovati et al. 1996). Studies were inadequate for the development of an MRL. Doses administered in animal studies were well above levels which produce toxic effects in ‘humans. In addition, multiple doses were not administered and a dose-response relationship could not be assessed. Additional well designed animal studies on the respiratory and systemic effects following intermediate-duration exposure, and the relevance of the effects to exposed humans, would be useful.

Chronic-Duration Exposure and Cancer. There are limited data on chronic occupational exposures to sulfur dioxide. These studies indicate a potential association between sulfur dioxide exposure and respiratory effects (lung cancer and lung function changes). However, these occupational studies have limitations concerning accurate exposure assessments and concomitant exposures. Epidemiological studies on the relationship between ambient air pollution and lung cancer (Ponka et al. 1993; Tango 1994), although limited, have suggested that the risk of lung cancer from sulfur dioxide exposure in the environment is nonsignificant. Epidemiological studies of children and acute air episodes of sulfur dioxide are confounded by the presence of other air pollutants that are also associated with lung function changes. Additional

supporting data from well-designed epidemiological studies would be useful. There are no known data on chronic human oral or dermal exposures to sulfur dioxide. Oral and dermal routes may be clinically relevant to humans, but inhalation is the primary route of concern. Therefore, oral and dermal data should not be high priority.

There are only a few limited chronic inhalation studies in two species of animals. No effects on lung function were observed in guinea pigs exposed to 5.72 ppm sulfur dioxide for 22 hours/day, 7 days/week, for 52 weeks (Alarie et al. 1972). Likewise, no lung function changes or histopathological alterations in the lung were observed in monkeys exposed to 5.12 ppm sulfur dioxide for 23.3 hours/day, 7 days/week, for 78 weeks (Alarie et al. 1975). Additional chronic-duration animal studies following inhalation exposure would be useful for providing supporting data regarding potential chronic-duration effects of sulfur dioxide. The chronic-duration studies are too limited to be used for developing a chronic-duration inhalation MRL; because only one dose was administered, a dose response relationship could not be assessed.

Several epidemiological studies were conducted to address cancer associated with occupational or environmental exposure to sulfur dioxide pollution, but definitive conclusions could not be drawn because of confounding factors (Bond et al. 1986; Enterline et al. 1987; Lubin et al. 1981; Ponka et al. 1993; Tango et al. 1994; Welch et al. 1982). A chronic cancer study in mice was also limited due to small sample size and the administration of only one dose. Well-designed studies which evaluate carcinogenicity potential following inhalation exposure in additional species are needed. Oral and dermal exposure studies are not of high priority because inhalation is the primary route of concern

Genotoxicity. *In vivo* clastogenic effects of sulfur dioxide in humans have been reported. Increases in chromosome aberrations and sister chromatid exchanges were detected in lymphocytes from 42 workers who were occupationally exposed to an average concentration of 41.7 mg/m^3 (15.9 ppm) of sulfur dioxide, a level which is eight times greater than the TLV (Yadav and Kaushik 1996). Similar findings have been observed in other studies of workers (Meng and Zhang 1990a; Nordenson et al. 1980). In addition, increases in the frequencies of lymphocytes with micronuclei were noted (Meng and Zhang 1990b). One study of potential chromosomal abnormalities in workers exposed to 8-hour workshift levels of about 1 ppm (2.62 mg/m^3) sulfur dioxide in the aluminum industry revealed that sulfur dioxide was without effect (Sorsa et al. 1982). Studies which examine genotoxic effects in animals following inhalation exposure were not located but would be useful Studies with animal germ cells have indicated that genotoxicity is possible following *in vitro* exposure but unlikely from intraperitoneal administration of sulfur dioxide metabolites (Jagiello et al. 1975;

Russell and Kelly 1975). Further human and animal studies to explore possible dose-response relationships and to provide mechanistic data would be useful.

Reproductive Toxicity. In a cross-sectional study of spontaneous abortions in an industrial community in Finland, no evidence was found that would associate sulfur dioxide exposure with a risk of spontaneous abortions (Hemminki and Niemi 1982). However, abnormalities in sperm have been associated with sulfur dioxide, as a surrogate of all air pollutants, in a limited study conducted in the Czech Republic (Selevan et al. 1995).

Reproductive effects were not observed in rats exposed to 5-30 ppm sulfur dioxide for 9 days prior to mating until 12-14 days of pregnancy (Petruzzi et al. 1996) in mice exposed to 25 ppm sulfur dioxide 7 hours/day on gestation days 6-15 or in rabbits exposed to 70 ppm sulfur dioxide 7 hours/day on gestation days 6-18 (Murray et al. 1979). The studies are limited because the reproductive function of the offspring were not assessed. A well-designed multigeneration reproductive study would be useful to assess the potential reproductive toxicity of sulfur dioxide. Because inhalation is the primary route of concern, oral and dermal exposure studies should not be a high priority.

Developmental Toxicity. There is evidence of an association between environmental exposure to sulfur dioxide during pregnancy and reduced birth weight. Like other epidemiological studies of air pollution mixtures, interpretation of the results is complicated by confounding factors such as other air pollutants and a lack of personal exposure information. Though additional, well-designed epidemiological studies would be useful, separation of effects associated with individual components of an air pollution mixture is unlikely considering the currently available technology.

Numerous developmental studies have been conducted in animals. One study reported no developmental effects in the offspring of pregnant mice that were exposed to 32-250 ppm sulfur dioxide on gestation days 7-17 (Singh 1982). In another developmental study in mice in which pregnant females were exposed to 32 ppm or 65 ppm on gestation days 7-18, increased time for righting reflex on postnatal day 1 and increased negative geotaxis on postnatal day 10 were reported (Singh 1989). The duration of exposure for each day was not stated. No visible signs of maternal toxicity and no effect on the number of live births were observed. Sulfur dioxide at a concentration of 65 ppm significantly decreased the birth weight (about 89% of controls) of the pups. Minor skeletal variations were reported in offspring of mice exposed to 25 ppm sulfur dioxide 7 hours/day on gestation days 6-15 and rabbits exposed to 70 ppm sulfur dioxide 7 hours/day on

gestation days 6-l 8 (Murray et al. 1979). Fetal body weights were also lower in exposed mice. Reduced food intake was the only sign of maternal toxicity. Neurological effects were not observed in the offspring of mice exposed to 5-30 ppm sulfur dioxide for 9 days prior to mating until 12-14 days of pregnancy (Petruzzi et al. 1996). Studies which examine developmental effects following oral or dermal exposure should not be high priority since inhalation is the primary route of concern.

Immunotoxicity. Epidemiological studies have indicated that sulfur dioxide air pollution may increase the prevalence of allergies (Soyseth et al. 1996) and incidence of respiratory infections (French et al. 1973) in children. However, both studies were limited by inadequate control of confounding factors and a lack of personal exposure data. Increased sensitization to antigen was reported in a study of guinea pigs exposed by inhalation to sulfur dioxide (Riedel et al. 1992). In an acute-duration inhalation study with hamsters, there was a significant reduction in endocytosis by pulmonary macrophage following exposure to 50 ppm sulfur dioxide for 4 hours while exercising (Skornik and Brain 1990). However, pulmonary defense mechanisms were not affected in rats and mice exposed to 0.32-0.43 ppm sulfur dioxide together with 87-113 $\mu g/m^3$ sulfate for 4 hours prior to or 17 hours following infection with Stuphylococcus aureus or Group C *Streptococci* (Goldstein et al. 1979). Additional studies to determine if inhalation of sulfur dioxide increases susceptibility to infection or allergen sensitization in humans or animals would be useful. Because inhalation is the primary route of concern, studies of oral or dermal exposure should not be high priority.

Neurotoxicity. One study has indicated that reflex response times may have been affected in workers exposed to sulfur dioxide, and was most likely due to a psychological response to systemic toxicity (Kehoe et al. 1932). Seizures and prostration were observed in rats following exposure to 2,350,50,000 and 500,000 ppm sulfur dioxide for an average of 176 minutes, <10 minutes, and <2 minutes respectively (Cohen 1973). Lipid peroxidation has been observed in the brains of guinea pigs exposed to sulfur dioxide for 1 hour/day for 30 days (Haider et al. 1982). Additional neurotoxicity studies would be useful to characterize the effects of sulfur dioxide on the nervous system.

Epidemiological and Human Dosimetry Studies. There are several epidemiological studies that have examined the potential association between respiratory effects (i.e., lung cancer and lung function changes) and inhalation exposure to sulfur dioxide (Agocs et al. 1997; Archer and Gillan 1978; Buchdahl et al. 1996; Dockery et al. 1982; Dodge et al. 1985; Lebowitz et al. 1979; Lowe et al. 1970; Shy et al. 1973; Skalpe 1964; Smith et al. 1977). There are also epidemiological studies that have examined the association between daily acute mortality and sulfur dioxide exposure (Anderson et al. 1996; Bacharova, 1996; Ballester

et al. 1996; Katsouyanni et al. 1997; Loomis et al. 1996; Mazumdar et al. 1982; Moolgavkar et al. 1995a, 1995b; Spix, 1996; Sunyer et al. 1996; Thurston et al. 1989; Touloumi et al. 1996; Verhoeff et al. 1996). Reproductive effects have also been examined in epidemiological studies (Selevan et al. 1995; Wang et al. 1997). However, these epidemiological studies are limited by confounders. Further studies that employ more precise measurements of exposure, control of exposure to other chemicals, and follow-up of occupational cohorts would be useful. Monitoring of populations around industrial areas where there are exposures to peak levels of sulfur dioxide would also be useful.

Biomarkers of Exposure and Effect

Exposure. No specific biomarkers of exposure for sulfur dioxide have been identified. Potential biomarkers include plasma *S*-sulfonate levels and urinary levels of sulfate (Balchum et al. 1960a; Frank et al. 1967; Kleinman 1984; Speizer and Frank 1966; Yokoyama et al. 197 1). Further studies examining the suitability of these potential biomarkers would be useful.

Effect. No specific biomarkers of effect for sulfur dioxide have been identified. Potential nonspecific biomarkers include lung function changes (EPA 1994a, 1994b; Sheppard et al. 1981) and clastogenic effects (Meng and Xhang 1990a, 1990b; Yadav and Kaushik 1996), leukocytes in bronchioalveolar lavage fluid (Sandstrom 1989a, 1989b), or adduct formation in nasal mucosa (Topinka et al. 1995). Further studies examining the suitability of these potential biomarkers, and identification of potential specific biomarkers, would be useful.

Absorption, Distribution, Metabolism, and Excretion. Sulfur dioxide, a highly water-soluble gas, is rapidly absorbed by the mucosa of the nose and upper respiratory tract (Kleinman 1984; Speizer and Frank 1966). Absorption in the lower respiratory tract is increased with enhanced ventilation associated with a transition from nasal to oronasal breathing (EPA 1986d). Absorbed sulfur dioxide metabolites are taken up by the blood and are readily distributed throughout the body (Balchum et al. 1960a; Frank et al. 1967; Yokoyama et al. 1971). Once absorbed, sulfur dioxide is rapidly metabolized to sulfates in the liver by the enzyme, sulfite oxidase (Gunnison et al. 1987) or through the generation of sulfur trioxide radical intermediate (Constantin et al. 1996). Sulfur dioxide may also react with proteins to form *S*-sulfonate (Gunnison and Palmes 1974). Sulfur dioxide is excreted primarily in the urine as sulfate. There is also evidence that glutathione is involved in the detoxification of sulfur dioxide (Kagadel et al. 1986; Langley-Evans et al. 1996). Studies which compare the quantitative distribution of sulfur dioxide within the

respiratory tract during nasal, oronasal, and oral breathing would be useful. Studies which examine the relationship between sulfite oxidase activity and levels of sulfur dioxide metabolites in blood would also be helpful. Identification of additional factors involved in the metabolism of sulfites would also be useful information.

Comparative Toxicokinetics. There are no studies that directly compare the toxicokinetics across species. PBPK models have not been developed. Sulfite oxidase activity varies among species. Therefore, studies providing quantitative data necessary to develop PBPK models would be useful.

Methods for Reducing Toxic Effects. Other than removing the subject from exposure, there is no specific method to reduce the absorption of sulfur dioxide. There are no known methods for specifically reducing the body burden of sulfur dioxide. Supportive treatment includes administration of 100% humidified supplemental oxygen with assisted ventilation as recprired, endotracheal intubation or tracheostomy if upper airway obstruction is present, and the use of inhaled sympathomimetic bronchodilators for bronchoconstriction (HSDB 1998). Studies examining methods to enhance the oxidation of sulfur dioxide to increase elimination might be useful. Studies to determine effects of antioxidant therapy in humans may also be useful.

Children's Susceptibility. Clinical studies have indicated that compared to healthy senior citizens, healthy adolescents are not at increased risk of respiratory effects following inhalation of sulfur dioxide (Koenig et al. 1982b; Rondinelli et al. 1987). Epidemiological studies indicate associations between sulfur dioxide pollution and respiratory symptoms (Buchdahl et al. 1996; Dodge et al. 1985; WHO 1979) and transient effects on respiratory function in children (Dockery et al. 1982; Shy et al. 1973). However, such studies are limited due to confounding effects of other air pollutants. Asthmatics in general are most susceptible to sulfur dioxide exposure, but it is not known if asthmatic children are more sensitive than asthmatic adults (EPA 1994a, 1994b). It is unlikely that additional epidemiological studies would provide conclusive information. However, additional controlled studies in asthmatic and healthy children would be useful in determining doses which produce effects, and whether these children are more susceptible to sulfur dioxide-induced respiratory effects than asthmatic and healthy adults. Controlled studies in young versus mature animals would also be useful.

Studies in humans and animals indicate that serious developmental effects are not likely from maternal inhalation of sulfur dioxide. However, developmental delays, such as reduced birth weight in humans and

decreased fetal weight and delayed ossification in animals, have been observed (Murray et al. 1977, 1979; Wang 1997). Data requirements for developmental effects are discussed under the Developmental Toxicity heading of this section (2.11.2 Identification of Data Needs).

Metabolic studies have demonstrated reduced liver sulfite oxidase activity in young rats (Cohen 1974). Comparisons of sulfite oxidase activity in infants, children, and adults and also in young and mature animals would be useful. Measurement of liver sulfite oxidase activity in young versus mature animals of other species would also be useful. Studies in which liver sulfite oxidase activity in young and mature animals is compared in relation to blood levels of sulfates, sulfites, and *S*-sulfonates following sulfur dioxide inhalation would also be useful. Pharmacokinetic studies in dogs have demonstrated that following inhalation of radio-labeled sulfur dioxide, a small amount of radio-label reaches the ovaries and testes (Balchum 1959). Experiments to identify the sulfur dioxide metabolite present in gonads would be useful. Studies which examine pharmacokinetics in immature or pregnant animals were not identified. Studies which examine the distribution of sulfur dioxide metabolites in pregnant animals to determine if they cross the placenta or are transferred to breast milk might be useful. Accumulation in maternal tissues is not expected for sulfur dioxide or its metabolites due to its high water solubility. Studies which examine absorption, metabolism, distribution, and excretion in immature animals would also be helpful in evaluating the impact of sulfur dioxide exposure in children.

Studies of genotoxicity in germ cells have demonstrated that mutations and clastogenic effects occur with *in vitro* exposure but not *in vivo* exposure (Iagiello et. al. 1975; Russell and Kelly 1975; Shapiro et al. 1977). Although genotoxicity has been observed in lymphocytes of workers exposed to sulfur dioxide (Meng and Zhang 1990a, 1990b; Yadav and Kaushik 1996), available data in animals indicates that genotoxicity in germ cells is unlikely from exposure to sulfur dioxide metabolites (Russell and Kelly 1975). Inhalation studies in animals could be done to verify that genotoxicity in germ cells does not occur following inhalation exposure to sulfur dioxide.

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

2.11.3 Ongoing Studies

Ongoing animal, occupational, or epidemiological studies of the health effects of sulfur dioxide were not identified.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of sulfur dioxide is located in Table 3- 1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of sulfur dioxide is located in Table 3-2.

Table 3-1. Chemical Identity of Sulfur Dioxide

Characteristic	Sulfur dioxide	Reference
Synonyms	Sulphur dioxide; sulfurous anhydride; sulfur oxide; sulfurous oxide; sulfurous acid anhydride	HSDB 1998
Registered trade name(s)	No data	
Chemical formula	SO_2	HSDB 1998
Chemical structure	O=S=O	HSDB 1998
Identification numbers:		
CAS registry	7446-09-5	HSDB 1998
NIOSH RTECS	WS4550000	HSDB 1998
EPA hazardous waste	No data	
OHM/TADS	7216914	OHM/TADS 1998
DOT/UN/NA/IMCO shipping	UN1079	HSDB 1998
HSDB	228	HSDB 1998
NCI	No data	

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Sulfur Dioxide

Property	Sulfur Dioxide	Reference
Molecular weight	64.06	Lide 1993
Color	Colorless	Lide 1993
Physical state	Gas (or liquid)	Lide 1993
Melting point	-72.7°C	Lide 1993
Boiling point	-10°C	Lide 1993
Density	2.927 g/L (gas); 1.434 (liquid)	Lide 1993
Odor	Strong odor, suffocating	Lide 1993
Odor threshold:		
Water	No data	HSDB 1998
Air	Low: 1.175 mg/m^3 (0.45 ppm); high: 12.5 mg/m^3 (4.8 ppm); irritating: 5 mg/m^3 (1.9 ppm)	
Solubility:		
Water at 0°C	22.8 g/100 cc	HSDB 1998
Water at 20°C	11.3 g/100 cc	
Water at 90°C	0.58 g/100 cc	
Organic solvents	Acetic acid, alcohol, chloroform, ether, sulfuric acid	
Partition coefficients:		
Log K_{ow}	No data	
Log K_{oc}	No data	
Vapor Pressure	3000 mm Hg at 20°C	HSDB 1998
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	Nonflammable	HSDB 1998
Conversion factors	2.62 mg/m^3 = 1 ppm	IARC 1992
Explosive limits	No data	

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

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

4.1 PRODUCTION

Sulfur dioxide has been produced commercially from the following raw materials: elemental sulfur; pyrites; sulfide ores of non-ferrous metals; waste sulfuric acid and sulfates; gypsum and anhydrite; hydrogen sulfide-containing waste gases; and flue gases from the combustion of sulfurous fossil fuels (IARC 1992). It is most commonly produced by burning sulfur but can also be produced by burning pyrites in a special furnace or by purifying and compressing sulfur dioxide gas from smelting operations.

Sulfur dioxide has been produced by burning molten sulfur in a special burner with a controlled amount of air. The burner gas, free of dust and cooled, is dissolved in water in a series of two towers. In a third tower, the solution is sprayed at the top and flows down while steam is injected at the base. The gas issuing from the third tower is then cooled to remove most moisture and passed up a fourth tower against a countercurrent of sulfuric acid. The dried gas is liquefied by compression (IARC 1992).

Sulfur dioxide can also be recovered commercially by liquefying gas obtained during smelting of non-ferrous metals such as lead, copper, and nickel. Much of this smelter by-product is recovered and oxidized to sulfur trioxide for producing sulfuric acid. Sulfur dioxide recovery, however, usually occurs only for environmental reasons (IARC 1992).

Sulfur dioxide was produced for sale at levels of 64,000 tons in 1960,99,000 tons in 1970, 124,000 tons in 1980, and 227,000 tons in 1987. Production was 1.39×10^{11} g in 1977, 1.18×10^{11} g in 1982, and 1.18×10^{11} g in 1985 (HSDB 1998). Most of the sulfur dioxide produced is for captive use in the sulfuric acid and wood pulp industries (IARC 1992). It is also used for refrigeration (HSDB 1998). The major producers of sulfur dioxide in 1989 included ChemDesign Corporation, Coulton Chemical Corporation, Dow Chemical, Hoeschst Celenese Corporation, Industrial Chemicals Corporation, Rhone-Poulenc, Inc., Tennessee Chemical Company, and Phelps Dodge Corporation (HSDB 1998).

4.2 IMPORT/EXPORT

Imports of sulfur dioxide were $5.17x10^{10}$ g in 1977, $2.26x10^{10}$ g in 1982,$2.33x10^{7}$ g in 1985, and $5.72x10^{7}$ kg in 1986 (HSDB 1998). The U.S. import of sulfur dioxide was 68,772,164 kg in 1994 (NTDB 1996).

Exports of sulfur dioxide were $1.62x10^{9}$ g in 1978, $5.38x10^{9}$ g in 1983, $1.60x10^{9}$ gin 1985, and $8.54x10^{7}$ g in 1987 (HSDB 1998). The U.S. export of sulfur dioxide was 1,173,002 kg in 1996 (NTDB 1996).

4.3 USE

Sulfur dioxide has numerous commercial uses which are based on its function as an acid, as a reducing or oxidizing agent, or as a catalyst. Sulfur dioxide is used in large quantities as a captive intermediate in the production of sulfuric acid and in the pulp and paper industry. Other common uses of sulfur dioxide include the following: fumigant, preservative, bleach, and steeping agent for grain in food processing; catalyst or extraction solvent in the petroleum industry; flotation depressant for sulfide ores in the mining industry; intermediate for bleach production; and reducing agent in several industrial processes (IARC 1992).

4.4 DISPOSAL

Sulfur dioxide is listed as a toxic substance under Section 3 13 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Super-fund Amendments and Reauthorization Act (SARA) (EPA 19988). Disposal of wastes containing sulfur dioxide is controlled by a number of federal regulations (see Chapter 7).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Sulfur dioxide has been identified in at least 16 of the 1,467 current or former EPA National Priorities List (NPL) hazardous wastes sites (HazDat 1998). However, the number of sites evaluated for sulfur dioxide is not known. The frequency of these sites within the United States can be seen in Figure 5-l.

Atmospheric sulfur dioxide is formed as a by-product of the combustion of fuel from power generation and industrial activities, and by the oxidation of reduced gases in the atmosphere. Volcanic activity also contributes to the levels of atmospheric sulfur dioxide. The atmospheric lifetime of sulfur dioxide is about 10 days (IARC 1992).

Sulfur dioxide is oxidized rapidly by both homogeneous and heterogeneous reactions and is removed from the atmosphere by precipitation and by dry deposition on surfaces, mainly as sulfuric acid.

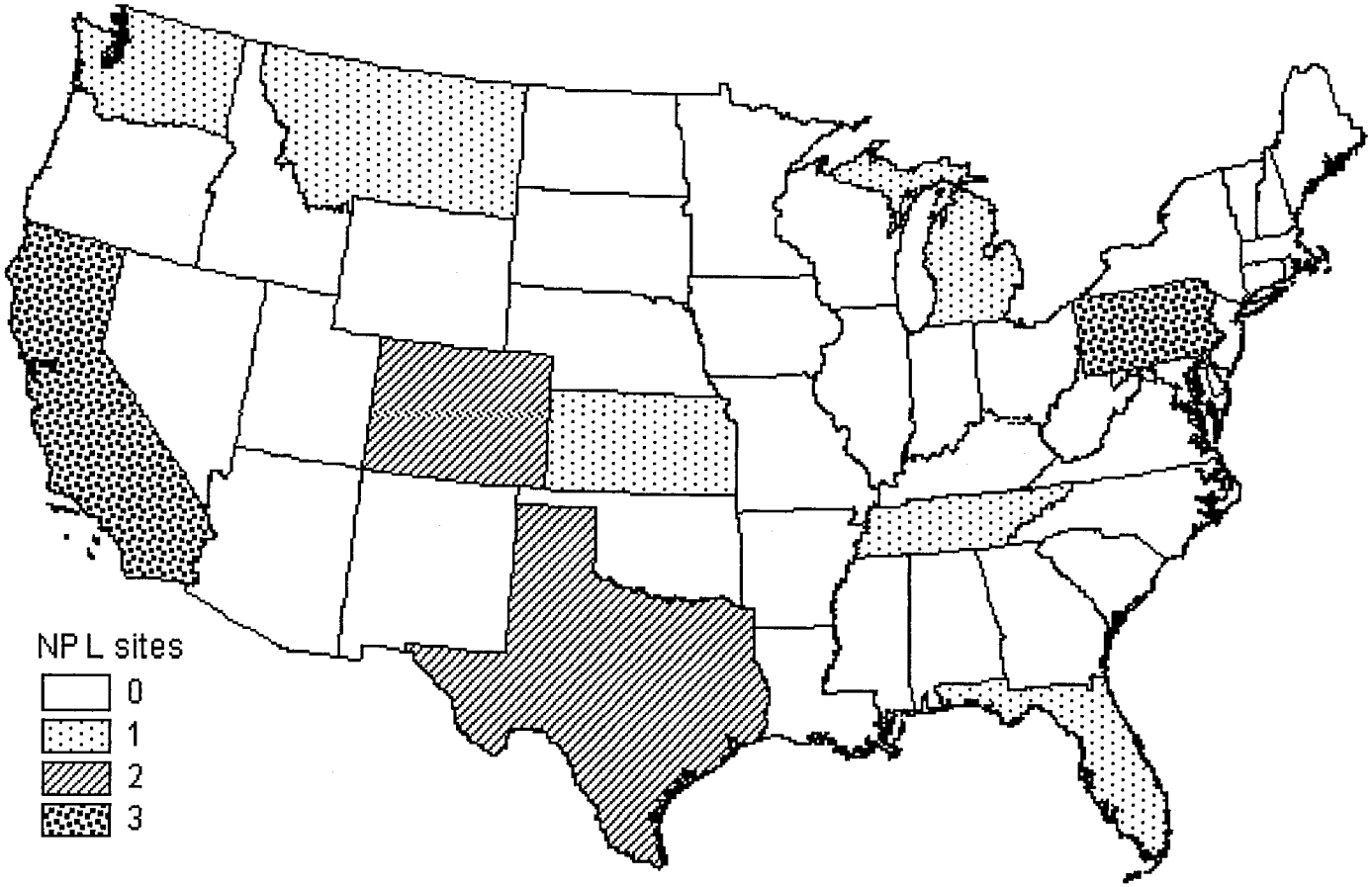
Inhalation of sulfur dioxide, by the general population residing near industrial sources and by workers exposed to sulfur dioxide, is generally the main route of human exposure to the chemical.
It should be noted that the amount of sulfur dioxide detected by chemical analysis is not necessarily the amount that is bioavailable.

5. 2 RELEASES TO THE ENVIRONMENT

Releases of sulfur dioxide to the environment from large processing facilities are not required to be reported to the Toxics Release Inventory (TRI).

Releases of sulfur dioxide are not required to be reported under SARA Section 3 13. Consequently, there are no data for this compound in the current TRI. Sulfur dioxide has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 16 of the 1,467 NPL hazardous waste sites (HazDat 1998).

Figure 5-1. Frequency of NPL Sites With Sulfur Dioxide Contamination



* Derived from HazDat 1998

5.2.1 Air

Releases of sulfur dioxide to air from large processing facilities are not required to be reported to the Toxics Release Inventory (TRI).

Sulfur dioxide has been identified in air samples collected at 8 of the 16 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1998).

Atmospheric sulfur dioxide, a major oxide of sulfur, can be formed from both anthropogenic and natural sources. On a global scale, the total annual atmospheric flux of sulfur has been estimated to be 140-350 million tons (of which less than 30% is anthropogenic sulfur) in the form of sulfur dioxide, sulfuric acids, and sulfate (HSDB 1998). The primary anthropogenic source of sulfur dioxide gas is fuel combustion from power generation and industrial processes. Fossil fuel accounts for 75-85% of man-made sulfur dioxide emissions on a global scale; industrial processes such as refining and smelting account for the remainder (HSDB 1998). Almost all of the man-made sulfur dioxide emissions (93.5%) are released in the Northern Hemisphere (HSDB 1998). With regard to the United States, EPA National Air Pollutant Emission Trends estimate that in 1994 a total of 2 1.1 million tons of sulfur dioxide was emitted into the atmosphere in the United States from point and area sources (EPA 1994a). The Air Toxicities Program is striving to reduce toxic air pollutants emissions in the United States by 1.5 million tons annually over the next 10 years (EPA 1995). Of the total sulfur dioxide emissions, about 18.5 million tons or 87.6% was attributed to fuel combustion, of which electricity utilities and industrial combustion constituted about 70% and 14%, respectively (EPA 1994a). The Utility Air Toxicities Study examines hazardous air pollutant emissions from coal, oil, and gas (fossil fuel) electric utilities and associated public health hazards. The predictions for the next two decades are a 30% increase in hazardous air pollutant emissions from coal utilities and a 50% decrease in emissions from oil utilities (EPA 1995). Sulfur dioxide emission from fuel combustion have come primarily from coal burning, with coal combustion producing 96% of the electric utility emissions. A similar trend was observed in England (Lee and Longhurst 1993), but not in Denmark where road traffic was considered the most prevalent source of air pollution for sulfur dioxide (Jensen and Fenger 1994).

According to EPA’s National Air Pollutant Emission Trends (EPA 1994a), other sources of sulfur dioxide include emissions from chemical and allied product manufacturing, metal processing, petroleum and related industries, other industrial processes, and on-road vehicles. These sources are, however, of less importance

as they collectively contributed less than 13% of the total emissions (EPA 1994a). Since sulfur dioxide is the major substance used for manufacturing sulfuric acid, it is not surprising that a significant source of industrial emissions is acid manufacturing and processing facilities.

Data are available at the state-level for sulfur dioxide emissions and rank by major category (EPA 1994a). Ohio and Indiana ranked first and second in the total sulfur dioxide emissions. Fuel combustion for electrical utilities accounted for the greatest portion of total emissions in all states. On the national level, sulfur dioxide emissions have shown a steady decrease in the United States since the 1970s (EPA 1994a; Lefohn and Shadwick 1991).

A study was conducted among 24 United States communities to study air pollution patterns (Spengler et al. 1996). A strong correlation between particle mass and sulfate concentrations and sulfate and hydrogen ion concentrations was found in Ohio, Pennsylvania, Virginia, West Virginia, Tennessee, and Kentucky. Concentrations in these areas ranged between 85 and 126 nmol/m^3 in the summer, the highest being in Ohio, Pennsylvania, and Kentucky. Due to the meteorological conditions, acidic pollution is highest during summer months in these areas. Sulfur dioxide is converted to acid sulfates without the presence of ammonia during this time (Spengler et al. 1996).

The Acid Rain Program projects a 40% reduction in SO_2 annual emissions in the United States between 1980 and 2010. The U.S. Geological Survey reports a 10 to 25% reduction in acidic rainfall because of a decline in emissions due to the Acid Rain Program. This reduction in emissions will also contribute to less sulfate haze (EPA 1995).

Volcanoes are a sporadic, but significant, natural source of sulfur dioxide. It has been estimated that $1.5x10^6$ tons of sulfur dioxide per year were evolved from worldwide volcanic production between the years 1500 and 1914 (Kellogg 1972). This estimate is about two orders of magnitude lower than the total annual sulfur dioxide liberated to the atmosphere (Kellogg 1972).

5.2.2 Water

Releases of sulfur dioxide to water from large processing facilities are not required to be reported to the Toxics Release Inventory (TRI).

Sulfur dioxide is very soluble in water, and the oceans are generally considered to be a sink for sulfur dioxide (Kellogg 1972). Surface water bodies can receive sulfur dioxide from the atmosphere by dry and wet deposition, from surface runoff, and from subsurface drainage (HSDB 1996; IARC 1992; Kellogg 1972; WHO 1979). It has been estimated that 70% of sulfate in rainwater comes from the washout of sulfur dioxide (Kellogg 1972). Hydrogen sulfide present in the oceans is probably oxidized to sulfur dioxide within hours (HSDB 1998). Rivers can transport sulfur compounds to the oceans (HSDB 1996).

It is possible that oceans may be a source of sulfur dioxide, especially during conditions when the equilibrium vapor pressure of sulfur dioxide in surface water exceeds the partial pressure of sulfur dioxide in the air immediately above it (Kellogg 1972). Sea salt can contribute to atmospheric levels of sulfate (Kellogg 1972).

There is no information on releases of sulfur dioxide to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

5.2.3 Soil

Releases of sulfur dioxide to soil from large processing facilities are not required to be reported to the Toxics Release Inventory (TRI).

Sulfur dioxide has been identified in soil and sediment samples collected at 5 of the 16 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1998).

Atmospheric sulfur dioxide can be removed by diffusion to the soil (Kellogg 1972). Sulfur uptake is dependent upon soil pH and moisture content (Kellogg 1972). One estimate of the uptake of sulfur dioxide by soil and vegetation is 52×10^{6} tons per year (Kellogg 1972). A rate of diffusion of 0.9×10^{-12} g/s cm^2/second has been calculated for the Northern Hemisphere (Kellogg 1972).

There is no information on releases of sulfur dioxide to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Anthropogenic and natural releases of sulfur dioxide to the environment are considered to be primarily to the atmosphere (HSDB 1998; Kellogg 1972; WHO 1979). Because of its high vapor pressure (3,000 mm Hg at 20°C), sulfur dioxide is typically present in a gaseous phase Some of the sulfur dioxide emitted into the air moves unchanged to various surfaces including soil, water, grass, and vegetation in general (WHO 1979). In the atmosphere, sulfur dioxide can be transformed into sulfuric acid or sulfates by a variety of processes (WHO 1979).

A field deposition study in Canada was conducted to measure the effects of atmospheric stability, rainfall intensity, and wind speed and direction on SO_2 deposition. The object was to compare the field data with the modeled results from a computation of the SO_2 contamination and accumulation by forests downwind from an SO_2 source. The highest levels of SO_2 deposition were found along the north-south direction and low levels were found along the northwest direction. This is due to the fact that the wind direction from northsouth is consistent with neutral weather, and wind direction from northwest is consistent with rainy weather and airborne SO_2 scavenging. The final results show that the field data is comparable to the modeled data; the modeled results accurately describe the deposition patterns in relation to the weather patterns and is therefore considered a reliable source (Bouque et al. 1996).

Sulfur dioxide is very soluble in water, and oceans are generally considered to be a sink for sulfur dioxide (Kellogg 1972). It is also possible that oceans can be a source of sulfur dioxide if the equilibrium pressure of sulfur dioxide in surface water exceeds the partial pressure of sulfur dioxide in the air immediately above it. Any potential releases of sulfur dioxide from water would be expected to partition to the atmosphere as discussed in Section 5.3.2.1 (Kellogg 1972; WHO 1979).

Soil can absorb sulfur dioxide, with uptake being dependent on the pH and moisture content of the soil (HSDB 1998). No data were found pertaining to soil adsorption and mobility of sulfur dioxide in soil. Hill (1971) studied absorption of several gaseous air pollutants by plants and found that the removal rates were in the following order: hydrogen fluoride (HF) > sulfur dioxide (SO_2) > chlorine (Cl_2,) > nitrogen dioxide (NO_2) > ozone (O_3) > peroxyacetyl nitrate (PAN) > nitric oxide (NO) > carbon monoxide (CO).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Sulfur dioxide may be oxidized to sulfur trioxide (SO_3) and sulfate in air photochemically or catalytically (Bufalini 1971; Radojevic 1992). The oxidations generally involve homogeneous-phase reactions (oxidation in the gas phase) and heterogeneous gas-solid reactions (oxidation on the surface of particles). Gas-phase reactions include direct photochemical oxidation of sulfur dioxide and oxidation by reacting with other gases and substances, including O, O^-_2, O_3 NO, NO^-_2 NO_3 N_2O_5 OH, hydrocarbons, or some heavy metal ions. In the direct oxidation pathway, sulfur dioxide gas molecules (at different electronically excited states due to solar irradiation) react with each other, forming SO_3, which may be further oxidized by other gases or water drops to form sulfate. Reaction pathways with other gases all result in similar end products: SO_3, or sulfate. Rate constants for sulfur dioxide oxidation by these gases vary from $2x\ 10^{-24}$ to $4x10^{-3}$ cm^3 $molecule^{-1}$ $second^{-1}$, with the reaction with N_2O_5 being the fastest (Radojevic 1992). Heterogeneous gas-solid reactions include oxidation of sulfur dioxide on the surfaces of activated carbons, metal oxides, and other particles.

Sulfur dioxide may be photochemically or catalytically oxidized to SO_3 and sulfate in air (Bufalini 1971; Radojevic 1992). The oxidations generally involve homogeneous-phase reactions (oxidation in gas or liquid phase) and heterogeneous gas-solid reactions (oxidation on the surface of particles). The atmospheric residence time of sulfur dioxide is about 10 days. Photochemical oxidation involves the reaction of sulfur dioxide with reactive molecules and free radical species, and with products of O_3 and alkene gases. Photochemical oxidation is thought to be initiated by absorption of solar irradiation energy. However, neither the detailed mechanism of this process nor the significance of this conversion process is clear. Photochemical oxidation was previously thought to be insignificant because the maximum conversion rate of sulfur dioxide was considered to be <0.04% h-l (Calvert et al. 1978; Radojevic 1992). However, much higher conversion rates (0.65% h-l) were reported by other researchers (Cox and Penkett 1970), and it was suggested that trace impurities in the ambient air may have contributed to this.

Sulfur dioxide can be oxidized by OH radicals in the gas phase relatively quickly, making it a major mechanism for sulfur dioxide conversion. This is a three-body addition reaction, and the conversion rates have been characterized to be >l% $hour^{-1}$ (Radojevic 1992).

In the atmosphere, aqueous-phase oxidation of sulfur dioxide can occur in cloud, fog, rain, deliquescent aerosol particles, and in surface liquid films on these particles (Benner et al. 1992; McKay 1971). Once dissolved in these droplets, sulfur dioxide may be oxidized to sulfate via a variety of mechanisms, thus forming "acid rain." Such a removal mechanism is commonly termed "wet deposition." The conditions under which this oxidation can be enhanced have been studied (Barrie and Georgii 1976). The investigators found that the absorption of sulfur dioxide was facilitated by manganese and iron ions, high solution pH, and high temperature. A decrease in temperature from 25 °C to 8°C resulted in a 5-l0-fold decrease in sulfur dioxide absorption rates. It was estimated that typical sulfur dioxide removal rates through this mechanism were between 0.08% and 2.0% hour-' depending on the manganese and iron concentrations and temperature. The catalytic oxidation of sulfur dioxide in the presence of iron and manganese was, however, not supported by Fung et al. (1991), who investigated the relative importance of three major aqueous reactions thought to be responsible for the in-cloud conversion of sulfur dioxide: oxidation of sulfur dioxide by H_2O_2 O_3 or O^-_2; in the presence of iron and manganese. They found that sulfate precipitation concentration is generally more sensitive to H_2O_2 than to O_3, and that the contribution of iron and manganese in the oxidation of sulfur dioxide by O^-_2 is insignificant. Some research has shown that catalyzed liquid-phase oxidation in the presence of iron and manganese is important in urban plumes and fogs where sulfur dioxide concentrations are sufficiently high; this oxidation may not be significant in cleaner, rural areas (HSDB 1998). The average overall conversion rate of sulfur dioxide (through all processes) to sulfate in Beijing was estimated to be 4.7% $hour^{-1}$ during the day and 3.4% $hour^{-1}$ during the night (Chen et al. 1990).

In a study of acid rain chemistry in the Allegheny Mountains, it was found that on average about half of the rain sulfate resulted from the scavenging of sulfur dioxide and the other half resulted from aerosol sulfate. Most of the rain acidity (-80%) arose from gases dissolved in cloudwater and rainwater (Pierson et al. 1987).

Sulfur dioxide can also be oxidized by some particles; this heterogeneous oxidation is affected by oxidants other than O;, temperature, and humidity. Particles that can react with and oxidize sulfur dioxide include carbonaceous metal oxides, atmospheric particles, and other particles (Radojevic 1992).

Sulfur dioxide can also be removed from air by uptake of plant leaves. It is reported that direct surface uptake of sulfur dioxide is the most significant dry removal process for atmospheric sulfur (HSDB 1998). A study of the absorption of several gaseous air pollutants by plants found that the removal rates were in the following order: hydrogen fluoride (HF) > sulfur dioxide (SO_2) > chlorine (Cl_2) > nitrogen dioxide (NO_2) > ozone (O_3) > peroxyacetyl nitrate (PAN) > nitric oxide (NO) > carbon monoxide (CO) (Hill 197 1).

5.3.2.2 Water

It has been known for a long time that sulfur dioxide in air can be oxidized to sulfate by cloud or rain droplets, thus forming "acid rain." Barrie and Georgii (1976) studied the conditions under which this oxidation can be enhanced. They found that the absorption of sulfur dioxide was facilitated by manganese and iron ions, high solution pH, and high temperature. A decrease in temperature from 25°C to 8°C resulted in a 5-10-fold decrease in sulfur dioxide absorption rates. It was estimated that typical sulfur dioxide removal rates through this mechanism were between 0.08% and 2.0% $hour^{-1}$, depending on the manganese and iron concentrations and temperature.

In addition to the above factors, oxidation of sulfur dioxide to sulfate is also affected by many dissolved gases. The oxidation normally involved reactions with dissolved H_2O_2,O^-_2,OH^-, HSO_3^{2-}, SO_4^{2-},H_3COOH,O_3, HO_2, NO^-_2 NO_3 NH_3 NH^+_4 NH^-_2 and peroxyacetyl nitrate (PAN), with some reactions catalyzed by F^{3+} or Mn^{2+} (Benner et al. 1992; McKay 1971). All of these reactions are dependent on solution pH because pH affects the solubility of sulfur dioxide. Benner et al. (1992) reported that oxidation of sulfur dioxide to sulfate was greatly enhanced when cloud droplets were exposed to sulfur dioxide and NH_3. Speculating that the enhanced surface oxidation may be true for NH_3, Benner et al. (1992) further studied the phenomenon and found that sulfur dioxide can be oxidized to sulfate only when NH_3, is present. This led to the conclusion that sulfur dioxide can be oxidized more rapidly in the presence of both sulfur dioxide and NH_3, compared to sulfur dioxide alone. Fung et al. (1991) determined the relative importance of three major aqueous reactions through which sulfur dioxide is oxidized to sulfate and found that oxidation by H_2O_2 was stronger than O_3, oxidation in light precipitation areas and was comparable in heavy precipitation areas. The contribution of catalytic oxidation of O_2^-; in the presence of manganese and iron was insignificant in any occasion.

The current practices in diluted acids disposal include discharging to waste-water treatment plants or neutralization by calcium hydroxide, which produces gypsum that can be reused. Stucki et al. (1993) developed an alternative disposal technique for sulfuric acid and a new combination of recycling processes. This technique involves reducing sulfuric acid to volatile weak acids by sulfate-reducing bacteria.

Dissolved sulfur dioxide in the surface layer of the ocean may be slowly oxidized to the sulfate anion (SO_4^{2-}) by the combined presence of dissolved O_2 and trace amounts of transition metal salts as catalysts (Kellogg 1972). At ocean depths, dispersed sulfate may be reduced to sulfur dioxide, sulfur, and hydrogen sulfide by the action of bacteria (Kellogg 1972).

Sulfur dioxide absorbed by freshwater lakes is less rapidly oxidized than seawater because of the much lower salt content of freshwater (Kellogg 1972).

5.3.2.3 Sediment and Soil

Once on the ground, sulfur dioxide may be absorbed by soil, water, and snow-covers (HSDB 1998; WHO 1979). Although snow-covered surfaces are ineffective in absorbing gaseous and particulate sulfur compounds, the melted snowpack during spring can result in rapid, short-term inputs of high sulfate into fresh water.

Sulfur dioxide can be reduced to H_2S in heat- and alkali-treated sewage sludge by the sulfate-reducing bacteria, *Desulfovbrio desulfuricans* or *Desulfotomaculum orientis* (Deshmane et al. 1993).

Acid rain is the leading cause in an increase in heavy metal mobility in soil. When soil is basic pH, heavy metals will form insoluble oxides or hydroxides of sulfate, and when soil is acidic, soluble sulfates will form (Grzesiak et al. 1997).

Hill (1971) and Garland et al. (1973) reported that vegetation could be an important sink for sulfur dioxide and several other air pollutants. Plants can absorb sulfur dioxide from air. Siebke et al. (1990) developed a model for simulating uptake and metabolism of sulfur dioxide by different leaf cell compartments.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to sulfur dioxide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on sulfur dioxide 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 sulfur dioxide in a variety of environmental media are detailed in Chapter 6 (Analytical Methods).

5.4.1 Air

Sulfur dioxide has been detected in urban, rural, and remote areas of the world (Kirk-Othmer 1978). Worldwide emissions of about 70.7 million tons of sulfur in the form of SO_2 were estimated for 1994 (O'Meara 1997). However, sulfur dioxide concentrations in the atmosphere display a very large range, depending on the intensity of industrial and urban development. It has been estimated that sulfur dioxide concentrations can range from 1 to 5 μg/m3 (0.0004-0.0019 ppm) in very remote clean areas to at least 6,000 $\mu g/m_3$ (2.29 ppm) in industrial areas (HSDB 1998). Trends show that in the United States between 1986 and 1995 the national composite SO_2 average decreased 37% and SO_2 emissions decreased 18%. Between 1994 and 1995 SO_2 emissions decreased 13% and mean national concentrations decreased 17% (EPA 1995). Spengler et al. (1990) reported that about 80% of U.S. sulfur dioxide emissions come from within the 31 states bordering on, or located east of the Mississippi River.

Higher concentrations of sulfur dioxide have been detected during forest fires and volcano eruptions. In response to a request from the Hawaii State Health Department, NIOSH made an assessment of exposure to lava and seawater emissions resulting from lava flowing into the sea, vaporizing the seawater, and releasing some toxic gases. Sulfur dioxide was detected at about 1.5 ppm in visible plumes (NIOSH 1992a). At the request of the National Park Services, NIOSH (1992b, 1992c) measured concentrations of several toxic gases at the personal breathing zone on July 18, 1991, as a result of a forest fire. Sulfur dioxide concentrations ranged from 0.6 to 3.0 ppm, with three samples above the evaluation criteria. On another occasion, firefighters' exposures to chemical contaminants during fire suppression operations were found to be as high as 9 ppm for sulfur dioxide (NIOSH 1991). These concentrations were close to or above the current NIOSH sulfur dioxide time-weighted-average (TWA) exposure limit of 2 ppm (NIOSH 1997) and above the shortterm exposure limit (STEL) of 5 ppm.

5.4.2 Water

No data were located regarding levels of sulfur dioxide monitored or estimated in water.

5.4.3 Sediment and Soil

No data were located regarding levels of sulfur dioxide monitored or estimated in sediment or soil.

5.4.4 Other Environmental Media

Sulfur dioxide can be taken up from the atmosphere by sulfate-treated plants. However, no estimates of the levels of sulfur dioxide are available (HSDB 1998). Sulfur dioxide has been detected in various foods and beverages (IARC 1992). Table 5-l summarizes the levels of sulfur dioxide in several foods and beverages.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Since sulfur dioxide is primarily present in gaseous form, the general public is exposed to it mostly by inhaling contaminated air. Exposures would be expected to be highest near industrial activities that involve fuel combustion. The well-known air pollution disaster that occurred in London in December of 1952 exemplifies the extent to which the general population has been exposed to adverse levels of sulfur dioxide in past years (IARC 1992; WHO 1979). Excess mortality was observed during this episode but several other contaminants were also present in air during the pollution episode. Other well-known examples of serious air pollution episodes include those that occurred in Meuse Valley, Belgium, and Donora, Pennsylvania (IARC 1992; WHO 1979). Table 5-2 summarizes ambient air levels of sulfur dioxide in various parts of the world.

Occupational exposures to sulfur dioxide are associated with workers in steel processing, refinery, and chemical plants. These workers are also frequently exposed to acid mists with increased risk of laryngeal cancer (Ahlborg et al. 1981; Forastiere et al. 1987; Soskolne et al. 1984; Steenland et al. 1988). It has been estimated that approximately 600,000 American workers may be occupationally exposed to sulfur dioxide (HSDB 1998). Some of the highest exposures occur when it is a by-product, as in the metal smelting industry, and in the processing or combustion of high-sulfur coal or oil (HSDB 1998).

Levels of occupational exposure vary from industry to industry. Sulfite pulp worker exposure fluctuates but reached levels greater than 10 ppm (26 mg/m^3) in the 1950s (studies in Finland, Norway, and the United States) (IARC 1992). Because of modernization of facilities and processes, these levels have been falling. Roasting of ores and the combustion of sulfur-containing fuels in the metal industries have resulted in workplace exposure concentration means of 1-10 ppm (2.6-26 mg/m^3) in copper smelters (studies in the following countries with corresponding years of measurement: Finland, 1951-1957; Sweden, date not specified; United States, 1940-1974, 1976, 1982) and 1 ppm (2.6 mg/m^3) or less in other operations. Occupational exposure levels with a mean >l ppm (2.6 mg/m^3) have been measured during sulfuric acid and superphosphate fertilizer manufacture as well as during firefighting (IARC 1992).

TABLE 5-1. Levels of Sulfur Dioxide in Various Foods and Beverages[a]

Food/beverage	Concentration of Sulfur Dioxide (ppm)
Onions, fresh	17
Onions, dried	60
Onions, canned, boiled	4
Onions, dried soup mix	10–30
Garlic, dried	121
Leak, dried soup mix	7
Soya bean protein, nonsulfited	20
Soya bean protein, sulfited	80–120
Cherries	24
Wine, white	14
Wine, burgundy	150

[a]IARC 1992

TABLE 5-2. Ambient Air Concentrations of Sulfur Dioxide in Different Parts of the World[a]

Location	Year	Sulfur dioxide concentration ($\mu g/m^3$)
Rural New York	1984–86	3.38–7.44 (0.0013–0.0028 ppm)
Pennsylvania	1983	26–31 (0.01–0.012 ppm)
Rural Pennsylvania	1984	3–131 (0.0011–0.05 ppm)
Bermuda	1982–83	0–1.67 (0–0.0006 ppm)
Coastal Delaware	1985	13.4 (0.005 ppm)
Bermuda (mid-ocean)	1985	0.7 (0.00027 ppm
Northwest Territories, Canada	November–December 1981	0.33–0.69 (0.00013–0.00026 ppm)
Northwest Territories, Canada	February 1982	2.3–4.3 (0.00088–0.0016 ppm)
Ontario, Canada	1982	8.4–16.2 (0.0032–0.0062 ppm)
Ontario, Canada	1984	0.1–62.8 (0–0.024 ppm)
Near H_2SO_4 producer, United Kingdom	1981	0.5–120 (0.0002–0.046 ppm)

[a]IARC 1992

Other probable exposure routes are dermal and/or eye contact (HSDB 1998). Since sulfur dioxide is an irritating, corrosive gas, direct dermal or ocular contact can cause immediate damage. The general public can also be exposed to sulfur dioxide through ingestion of some foods that contain it such as onion, garlic, and wine (see Table 5-1).

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983, an estimated 55,029 workers were potentially exposed to sulfur dioxide in the workplace (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of the number of workers potentially exposed to chemicals in the workplace.

No information was found regarding the number of people potentially exposed in the vicinity of hazardous waste sites. However, since sulfur dioxide has been found near hazardous waste sites, people living near them may be exposed to higher than background levels.

5.6 EXPOSURE OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in 2.6 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, and 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; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Sulfur dioxide is a common air pollutant, and children of all ages are therefore potentially exposed. Inhalation is the primary route of exposure and there are no known exposure pathways that are unique to children. Children living near NPL waste sites or in areas of heavy industry, such as those related to fuel combustion, metal processing, and paper manufacturing, are typically exposed to the highest concentrations

of sulfur dioxide. Levels of sulfur dioxide in air vary between 1-5 μg/m^3 (0.0003-0.002 ppm) in rural areas and 6,000 μg/m^3 (2.3 ppm) in industrial areas (HSDB 1998). Significant exposures are not anticipated through diet, household products, structural building materials, school activities, or the clothing, skin, or breath of occupationally exposed parents.

There are no known studies which report levels of sulfur dioxide or its metabolites in children, in maternal reproductive organs during pregnancy, or in breast milk. The weight adjusted intake of sulfur dioxide in children compared to adults is not known but may be greater. Children breath more air per kilogram of body weight than adults. Children exercise more frequently than adults (CDC 1996; Cureton 1987). Exercise increases breathing rate and results in both an increased dose of sulfur dioxide to the lower respiratory tract and enhanced pulmonary effects. Studies which measure weight-adjusted intake in children have not been identified.

Exposure to children can be reduced by limiting the time spent outdoors, especially during periods of high pollution levels. Studies in animals indicate that small quantities of sulfur dioxide metabolites reach the gonads following inhalation of sulfur dioxide. The chemical identity of the metabolites is not known (i.e., sulfite, *S*-sulfonate, sulfate), but animal studies indicate that genotoxic effects in germ cells are unlikely following inhalation of sulfur dioxide. There is no available information on whether sulfur dioxide metabolites are likely to cross the placenta or be transferred to breast milk.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to sulfur dioxide (see Section 5.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to sulfur dioxide. These populations include individuals living in proximity to sites where sulfur dioxide was produced or sites where sulfur dioxide was disposed of, and individuals living near one of the 16 NPL hazardous waste sites where sulfur dioxide has been detected in some environmental media (HazDat 1998).

Workers involved in industries in which sulfur dioxide is processed or produced are at a potential risk to high sulfur dioxide exposures. Some of the highest exposures occur during the processing or combustion of high-sulfur coal or oil. Members of the general population who live near urban areas with industrial activities related to the processing or combustion of high-sulfur fuels would be exposed to higher than background levels of sulfur dioxide.

5.8 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 sulfur dioxide is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of sulfur dioxide.

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.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. Adequate information is available on the physical and chemical properties of sulfur dioxide (HSDB 1998).

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986,42 USC. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

However, sulfur dioxide is not required to be reported to the TRI. There are some estimates of the release of sulfur dioxide to the environment from anthropogenic sources on a global scale. There are also some estimates of national emissions of sulfur dioxide (EPA 1994a). Additional information on the identification of the sources that are likely to produce 5-and 10-minute peak exposures to high concentrations of sulfur dioxide, as well as on the frequency of the occurrence of such peak exposures, would be useful.

The latest import information reported was for 1994 (NTDB 1996) and the latest export information was for 1996 (NTDB). More recent import/export information would be useful.

Environmental Fate. There are no accurate measurements of the releases of sulfur dioxide from natural sources such as volcanoes, the ocean, and biogenic sources (Kellogg 1972; WHO 1979). Crude estimates of the release of sulfur dioxide from natural sources have been based on the amount of sulfur required to balance the total sulfur budget (Kellogg 1972). Studies that can provide more accurate estimates of the releases of sulfur dioxide from natural sources would be useful. Also, additional information on the role of sulfur dioxide released from anthropogenic and natural sources in the formation of acid rain would be useful.

Releases of sulfur dioxide to the environment as a result of industrial activity are expected to be primarily to the atmosphere (WHO 1979). Atmospheric sulfur dioxide is formed as a by-product of the combustion of fuel from power generation and industrial activities, and by the oxidation of reduced gases in the atmosphere. Since water covers 70% of the earth's surface, biogenic gas emissions are the largest natural source of sulfur emissions to the atmosphere. Airborne sea spray and marine and coastal organisms are all responsible for introducing sulfur into the atmosphere. These emissions are estimated at 11.9 and 15.4 Tg S gases/year (Tg = teragrams = 10^{12}g; S = sulfur) according to the Department of Energy (DOE 1996). Volcanic activity also contributes to the levels of atmospheric sulfur dioxide (Kellogg 1972). Gas emissions by vulcanism have shown estimates which vary due to methods of measurement and vulcanism variability. The annual volcanic sulfur emissions range was between 0.75 and 42 Tg S. However, the more well known median estimates were 9-24 Tg S/year with the average annual value being ≥9 Tg S (DOE 1996). Sulfur dioxide is oxidized rapidly by both homogeneous and heterogeneous reactions and is removed from the atmosphere by precipitation and by dry deposition on surfaces, mainly as sulfuric acid. A 1983 study by Ryaboshapko found that, based on seasonality, area1 distribution, mixing height and other factors, annual global wind blown soil sulfur emissions were 3.3-10 Tg S/year with an average of 6.7 Tg S/year. These emissions are more significant for some arid and semi-arid regions (DOE 1996). Additional information on the half-life of sulfur dioxide in soils and water would be useful.

Bioavailability from Environmental Media. Sulfur dioxide is likely to be absorbed following inhalation of contaminated air. However, data are lacking on the bioavailability of sulfur dioxide following ingestion of contaminated soils and groundwater or foods grown in areas with contaminated air and water. This information would be useful in determining the importance of these routes of exposure.

Food Chain Bioaccumulation. No data pertaining to the potential of sulfur dioxide to bioaccumulate or biomagnify in the food chain were identified. This information would be useful in assessing the potential risks associated with the levels of sulfur dioxide in environmental media.

Exposure Levels in Environmental Media. Routine monitoring of sulfur dioxide levels in ambient air is currently being performed. However, the monitoring data are insufficient to allow adequate characterization of human exposure to 5- and 10-minute peak levels of sulfur dioxide.

Reliable monitoring data for the levels of sulfur dioxide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of sulfur dioxide in the environment can be used in combination with the known body burdens of sulfur dioxide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Occupational studies often do not report adequate exposure levels of sulfur dioxide. Additional information is needed on the exposure levels among populations living in the vicinity of hazardous waste sites.

There are several nonspecific biomarkers for sulfur dioxide exposure such as changes in respiratory function or plasma *S*-sulfonate levels. Additional studies to identify specific biomarkers may be useful for the characterization of exposure levels.

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

Exposures of Children. Children are primarily exposed to sulfur dioxide through inhalation of polluted air. There are no pathways which are unique to children and further studies on this subject are not necessary. The weight-adjusted intake in children is expected to be greater than adults because children breathe more air per kg of body weight and exercise more frequently. Exercise increases breathing rate, which results in a greater sulfur dioxide dose to the lower respiratory tract. Studies which measure sulfur dioxide intake in children as well as data on respiratory parameters, such as tidal volume and breathing rate, are required to determine actual exposure levels in children. The only way to reduce childhood exposure to sulfur dioxide is by limiting time spent outdoors during periods of high air pollution. Additional research for the prevention of exposure is not required.

Child health data needs relating to susceptibility are discussed in 2.11.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for sulfur dioxide were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance 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 this substance.

5.8.2 Ongoing Studies

Ongoing studies of the potential for human exposure to sulfur dioxide were not identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring sulfur dioxide, its metabolites, and other biomarkers of exposure and effect to sulfur dioxide. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is 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.

6.1 BIOLOGICAL SAMPLES

No methods for determining sulfur dioxide in biological materials were located. Most studies concerning human health effects measure the concentrations of sulfur dioxide in the air or in the water which surrounds the subject. The measurement of sulfur dioxide in biological materials is not a method commonly used because of the rapid conversion of sulfur dioxide to sulfur-containing metabolites. Biomarkers can be used to indirectly measure sulfur dioxide exposure. In a study by Gunnison and Palmes (1974), *S*-sulfonate levels in human plasma showed a positive correlation with atmospheric sulfur dioxide. However, the methods for detecting *S*-sulfonates in human plasma lacked sensitivity and precision (Gunnison and Palmes 1974). If *S*-sulfonate is confirmed as a biomarker of exposure to sulfur dioxide and as methods for determining Ssulfonate in human plasma become more sensitive, detection of S-sulfonates in human plasma may serve as an adequate method for determining exposure to sulfur dioxide.

6.2 ENVIRONMENTAL SAMPLES

Sulfur dioxide has been measured in air, in water, and in food and beverages. Methods for determining levels in the air include ion chromatography, titration, calorimetry, mass spectrometry, conductimetry, amperometric detection, flame photometric detection, and turbidimetry (see Table 6-l). Ion chromatography seems to be the most sensitive of these methods with a detection limit of 3 μg/sample for sulfur dioxide (NIOSH 1994a). Sulfur dioxide has also been measured in stack gases. Methods for measuring sulfur dioxide in stack gases

Table 6-1. Analytical Methods for Determining Sulfur Dioxide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect on cellulose filter saturated with Na_2CO_3 preceded by a cellulose ester membrane; oxidize sulfite to sulfate with H_2O_2; elute with $NaHCO_3/NaCO_3$.	IC	3 µg/sample	NR	NIOSH 1994a (Method 6004)
	Absorb in 0.3N H_2O_2; titrate using bromocresol green and methyl red solution.	Titration	Range 0.026–26 mg/m^3 (0.01–10 ppm)	NR	NIOSH 1977 (Method 146)
	Draw air through bubbler containing H_2O_2; add isopropanol; adjust pH with dilute HCl; titrate using 0.01M $Ba(ClO_4)_2$ and Thorin indicator.	Titration	3.4 mg/m^3 (1.3 ppm)	NR	EPA 1995k
	Absorb in potassium or sodium tetrachloro-mercurate; complex heavy metals with EDTA; treat with 0.6% sulfamic acid; treat with formaldehyde and para-rosaniline; read maximal absorbance at 548 nm.	Colorimetry	26 µg/m^3 (0.01 ppm)	NR	Kok et al. 1987b
	Adsorb onto Molecular Sieve 5A; desorb with heat.	MS	2 mg/m^3 (0.8 ppm)	NR	NIOSH 1977 (Method 146)

Table 6-1. Analytical Methods for Determining Sulfur Dioxide in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Remove particles by filtration; impinge air onto surface of hydrogen peroxide solution; record conductivity.	Conductimetry	139 µg/m^3 (~0.05 ppm)	>99	Adams et al. 1971; Nash et al. 1961
	Maintain constant current as sulfur dioxide reduces halogen to halide; measure current.	Amperometric detection	Range 26–5200 µg/m^3) (0.01–2 ppm)	NR	Kok et al. 1987c
	Collect on filter paper saturated with triethanolamine aqueous solution. Convert sulfur dioxide to sulfate.	IC	3.3 µg/m^3	NR	Dariusz et al. 1997
	Collect on fluoro-(aerosol) pore and Na_2CO_3 cellulose (gas) filter in tandem. Collect in bucket. Collect on filters and extract H_2O.	IC and colorimetry	–	–	Okita et al. 1996
	Collect on sodium carbonate treated filter and teflon particulate filter	IC uv/vis	0.14 µg/m^3	>95%	Karakas and Tuncel 1997
	Collect in a dilute solution of H_2O_2. Oxidize SO_2 to sulfate with H_2O_2.	IC	0.44 µg/mL	99%	Velasquez et al. 1996

Table 6-1. Analytical Methods for Determining Sulfur Dioxide in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Filter disks inserted into gas cell. Gas circulation on both sides. Fill cell with test gas.	FTIR	0.5 ppm	NR	Batterman et al. 1997
	Filter extracted in H_2O_2 ultrasonically. Filter and inject solution.	IC	10 ppb	–	Santis et al. 1997
Stack gases	Irradiate sample with pulsed ultraviolet light; pass emitted fluorescent light through broad-band optical filter; detect by photomultiplier tube	PFD	Range 2.6–13,000 mg/m^3 (1.0–4,962 ppm)	NR	Adams et al. 1987
	Collect via impinger (using controlled condensation method); titrate using sodium hydroxide and bromophenol blue indicator	AT	Range 26–15,600 mg/m^3 (10–6,000 ppm)	NR	Knapp et al. 1987
	Extract isokinetically; separate sulfuric acid mist (including sulfur trioxide) and sulfur dioxide; add isopropanol; titrate using 0.01M $Ba(ClO_4)_2$ and Thorin indicator	Titration	1.2 mg/m^3 (0.46 ppm)	NR	EPA 1995c

Table 6-1. Analytical Methods for Determining Sulfur Dioxide in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Gases	Sample drawn though filter and injected into an evacuated Saran gas bag	GC/TCD	125 ppm	–	Endecott et al. 1996
Gas (flue)	SO_2 removed when flue gas passes.	SNAP (SO_2/NO_2 adsorption process)	–	99	Anonymous 1996a
Gas	Filter pack- collected on NaOH (1% in MeOH) filters.	IC	0.1 µg S/m^3	NR	Makkonen and Juntto 1997
	Absorption solution - air drawn in prefilter and bubbled through 0.3% H_2O_2 solution (solution acidified by perchloric acid).	IC	0.02 µg/m^3	NR	
	Passive sampler - collected on 1% NaOH in MeOH filter.	Molecular diffusion	NR	NR	
Beer	Add mercury stabilizing solution and 0.1N H_2SO_4; add 0.1N NaOH; add para-rosaniline and formaldehyde solutions	Colorimetry	NR	NR	Helrich 1990
Food	Heat in refluxing HCl; add nitrogen gas stream; condense gas into 3% H_2O_2 solution; titrate with NaOH and methyl red indicator	Titration	10 ppm (26.2 mg/m^3)	NR	Kim et al. 1990

Table 6-1. Analytical Methods for Determining Sulfur Dioxide in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Heat in refluxing HCl; add nitrogen gas stream; condense into Na_2HPO_4/ D-mannitol solution; dilute	AD/IEC-EC	<10 ppm (26.2 mg/m^3)	NR	Kim et al. 1990
	Homogenize with buffer (pH 9) for 1 minute using Polytron; filter extract and immediately inject	AE/IEC-EC	<1 ppm (2.62 mg/m^3)	NR	Kim et al. 1990

AD = acid distillation; AE = alkali extraction; AT = alkalimetric titration; IC = ion chromatography; IEC-EC = ion exclusion chromatography with electrochemical detection; MS = mass spectrometry; NR = not reported; PFD = pulsed fluorescence detection; S = sulfur

include pulsed-fluorescence detection and titration (Adams et al. 1987; EPA 1995k). Sulfur dioxide is not found in water because it is reduced to sulfuric acid in water. Colorimetry, titration, and either acid distillation (AD) or alkali extraction (AE) ion exclusion chromatography (IEC) with electrochemical detection (ED) can be used to measure sulfur dioxide in food and beer (Helrich 1990; Kim et al. 1990). These methods are summarized below.

NIOSH recommends ion chromatography (Method 6004) for the determination of sulfur dioxide in ambient air (NIOSH 1994a). Method 6004 is specific for sulfur dioxide and is applicable to STEL samples; the working range is 0.5-20 mg/m^3 (0.2-8 ppm) for a 100-L air sample (NIOSH 1994a). Sulfur trioxide may give a positive interference for sulfur dioxide.

Sulfur dioxide can also be measured in the air and in stack gases by titration. After separation of sulfur dioxide and sulfuric acid, the quantity of sulfur dioxide can be measured by barium-thorin titration (EPA 1995k). Possible interferents are free ammonia, water-soluble cations, and fluorides.

Colorimetry has been used to measure sulfur dioxide in air and beer (EPA 1986a, 1986b; Kok et al. 1987a, 1987b). Calorimetric analyzers are simple and highly sensitive (Hollowell et al. 1973). Calorimetric analyzers measure a solution's optical absorbance spectrophotometrically; the absorbance is proportional to the concentration of the colored species. However, color intensity is sensitive to temperature, pH, development time, purity of reagents, age of solutions, and some atmospheric interferents. Specificity may improve with development time but does not allow a fast response (Hollowell et al. 1973).

Conductimetric analysis measures the increase in conductivity as sulfur dioxide is absorbed into a hydrogen peroxide solution. This method has also been used to measure sulfur dioxide in the air (Adams et al. 197 1). Conductimetric analysis is popular because it of its high sensitivity, fast response, minimal maintenance, and simple operation. The major disadvantage to conductimetric analysis is its susceptibility to interference by nonsulfur dioxide gases that form or remove ions (Hollowell et al. 1973).

Amperometric analyzers can also be used to measure sulfur dioxide in air. Amperometric analyzers measure the current necessary to maintain a constant concentration of titrant as sulfur dioxide reduces the titrant. This method needs minimal maintenance; however, this method is limited by interference from compounds that

react with the titrant (Hollowell et al. 1973). It is applicable to the determination of sulfur dioxide when other sulfur compounds or other interferents do not exceed 5% of the sulfur dioxide concentration (Kok et al. 1987c).

Sulfur dioxide emissions can be continuously detected and determined in stack gases by pulsed fluorescence (Adams et al. 1987). Sample gas is irradiated by pulsed ultraviolet illumination that has passed through an interference filter, while the 90° emitted fluorescent light is passed through a broad band optical filter (240-420 nm) and is detected by a photomultiplier tube. The emitted light is proportional to the concentration of the sulfur dioxide in the sample. Interference may be caused by a build-up of particulate matter and condensed water on all the surfaces in contact with the sample.

Alkalimetric titration is another method for the determination of sulfur dioxide in stack gases (Knapp et al. 1987). This method is applicable to the determination of sulfur dioxide in the range of 26-15,600 mg/m^3 (or 10-6000 ppm). Below these levels, the color change at the end point cannot be visually detected. This lack of sensitivity and the possible interference caused by ammonia, ammonia compounds, and fluorides limit the use of this method. Ion chromatography is much more sensitive and allows much lower detection limits for equivalent sample volumes or better time resolution (shorter sampling times) at the same detection limits.

Sulfur dioxide is used as a fungicide on grapes. Sulfite residues from this use are tolerated up to 10 ppm; however, it is important that adequate methods are available to measure levels that exceed 10 ppm. Three methods have been suggested for the determination of sulfite residues on grapes; however, AE/IEC-ED is the recommended method because it is rapid, straightforward, free from interference, and able to detect sulfite residues at levels far below the limit of tolerance (Kim et al. 1990).

6.3 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 sulfur dioxide is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of sulfur dioxide.

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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No specific methods for determining biomarkers of exposure and effect were identified. Potential biomarkers include plasma S-sulfonate levels and urinary levels of sulfate (Balchum et al. 1960a; Frank et al. 1967; Kleinman 1984; Speizer and Frank 1966; Yokoyama et al. 1971). Further studies examining the accuracy and reliability of these potential biomarkers would be useful.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available for measuring sulfur dioxide in air (EPA 1995k; NIOSH 1994a; WHO 1979). One difficulty in measuring environmental levels of sulfur dioxide is the interference from other air pollutants, in particular, other sulfur-containing compounds. Accurate methods that are specific to sulfur dioxide and that minimize interference from other sulfur-containing compounds would be useful. Also, research investigating the relationship between observed health effects and levels measured in air, water, soil, and sediment could increase our confidence in existing methods and/or indicate where improvements are needed.

6.3.2 Ongoing Studies

No ongoing studies of improved analytical methods were located for sulfur dioxide.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding sulfur dioxide in air, water, and other media are summarized in Table 7-1.

A NTP cancer classification has not been reported for sulfur dioxide. NTP has not conducted genetic toxicology or chronic toxicology and carcinogenicity bioassays on sulfur dioxide (ACGIH 1991).

A STEL for occupational exposure has been established at 5 ppm (10 mg/m^3). World Health Organization (WHO) guidelines for exposure to sulfur dioxide are listed in Table 7-l.

EPA primary and secondary NAAQS are listed in Table 7-1. A 24 hour limit and an annual limit of exposure have been established. However, despite the effects induced in exercising asthmatics by brief exposure to sulfur dioxide (Utell and Frampton 1992), no short-term ambient sulfur dioxide standard has been established.

An acute-duration MRL of 0.01 ppm has been derived based on increased airway resistance in asthmatics (Sheppard et al. 1981).

TABLE 7-1. Regulations and Guidelines Applicable to Sulfur Dioxide

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1992a
WHO	10-minute exposure limit	500 µg/m^3 (0.2 ppm)	WHO 1987
	1-hour exposure limit	350 µg/m^3 (0.13 ppm)	WHO 1987
	24-hour exposure limit	100–150 µg/m^3 (0.04–0.06 ppm)	WHO 1979
	Annual arithmetic mean	40–60 µg/m^3 (0.015–0.023 ppm)	WHO 1979
NATIONAL			
Regulations:			
a. Air:			
EPA	NAAQS, national primary ambient air quality standard for sulfur oxides measured as sulfur dioxide		EPA 1998a (40 FR 50.4)
	24-hour exposure limit[b]	365 µg/m^3 (0.14 ppm)	
	Annual arithmetic mean	80 µg/m^3 (0.03 ppm)	
	NAAQS, national secondary ambient air quality standard for sulfur oxides measured as sulfur dioxide		EPA 1998b (40 CFR 50.5)
	3-hour exposure limit[b]	1,300 µg/m^3 (0.5 ppm)	
OSHA	PEL TWA (8 hours)	13 mg/m^3 (5 ppm)	OSHA 1998 (29 CFR 1910.1000)
b. Water:			
EPA	Hazardous substance under the Clean Federal Water Pollution Control Act Section 311(b)(2)(A)	No	EPA 1998c (40 CFR 116.4)
c. Food:			
EPA	Residues from the use of sulfur dioxide in liquid grain-fumigant formulations for market or fire-retardant purposes at levels not exceeding 5% by weight are exempted from the requirement of a tolerance in or on barley, buckwheat, corn, oats, popcorn, rice, rye, grain sorghum, (milo), and wheat	Yes	EPA 1998e (40 CFR 180.1013)
	Residues of sulfur dioxide resulting from postharvest fungicial use are exempted from the requirement of tolerances in or on corn for feed us only (non-human consumption)	Yes	EPA 1998e (54 CFR 180.1013)

TABLE 7-1. Regulations and Guidelines Applicable to Sulfur Dioxide (*continued*)

Agency	Description	Information	References
NATIONAL (cont'd)			
	Tolerance for sulfite residues from the fungicide sulfur dioxide in or on the following raw agricultural commodity: grapes, postharvest	10 ppm (26.2 mg/m^3)	EPA 1998d (40 CFR 180.444)
FDA	Recognized as safe when used in accordance with good manufacturing or feeding practices except meats and food sources of vitamin B1	Yes	FDA 1995 (21 CFR 582.3862)
b. Other:			
DOT	Forbidden for transport on passenger-carrying aircraft or railcars	Yes	DOT 1998a (49 CFR 172.101)
	Domestic transportation labels, poison gas, corrosive	Yes	DOT 1998a
EPA	CERCLA reportable quantity	500 pounds	EPA 1998f (40 CFR 355 Appendix A)
	Extremely hazardous substance, TPQ	500 pounds	EPA 1998f (40 CFR 355 Appendix A)
EPA-OSW	Designation of hazardous substance	No	EPA 1998c (40 CFR 116.4)
Guidelines:			
a. Air:			
ACGIH	TLV TWA	5.2 mg/m^3 (2 ppm)	ACGIH 1998
NIOSH	REL TWA	5 mg/m^3 (2 ppm)	NIOSH 1997
	STEL	13 mg/m^3 (5 ppm)	NIOSH 1997
STATE[c]			
Regulations and Guidelines:			
a. Air:			
	Acceptable ambient air concentation:		
California	1-hour	0.25 ppm	CA ARB 1998
	24-hour	0.04 ppm	
Colorado	1°: 24-hour	260 µg/m^3 (0.10 ppm)	CO DPHE 1998
	Annual	75 µg/m^3 (0.03 ppm)	
	2°: 24-hour	60 µg/m^3 (0.02 ppm)	
	Annual	150 µg/m^3 (0.06 ppm)	
Connecticut	1°: 24-hour	365 µg/m^3 (0.14 ppm)	CO DPHE 1998
	Annual	80 µg/m^3 (0.03 ppm)	
	2°: 24-hour	1300 µg/m^3 (0.5 ppm)	
	Annual	360 µg/m^3 (0.1 ppm)	

TABLE 7-1. Regulations and Guidelines Applicable to Sulfur Dioxide (*continued*)

Agency	Description	Information	References
STATE (cont'd)			
Florida	3-hour	1300 µg/m^3 (0.5 ppm)	FL DEP 1998
	24-hour	260 µg/m^3 (0.1 ppm)	
	Annual	60 µg/m^3 (0.02 ppm)	
Maine	3-hour	1150 µg/m^3 (0.4 ppm)	ME DEP 1998
	24-hour	230 µg/m^3 (0.09 ppm)	
	Annual	57 µg/m^3 (0.02 ppm)	
Minnesota	1°: 24-hour	365 µg/m^3 (0.14 ppm)	MN PCA 1998
	Annual	80 µg/m^3 (0.03 ppm)	
	2°: 24-hour	365 µg/m^3 (0.14 ppm)	
	Annual	60 µg/m^3 (0.02 ppm)	
Montana	1-hour	0.5 ppm	MT DHES 1998
	24-hour	0.10 ppm	
	Annual	0.02 ppm	
Nevada	1°: 24-hour	365 µg/m^3 (0.14 ppm)	NV DCNR 1998
	Annual	80 µg/m^3 (0.03 ppm)	
	2°: 24-hour	1300 µg/m^3 (0.5 ppm)	
	Annual	260 µg/m^3 (0.1 ppm)	
New Mexico	24-hour[e]	0.10 ppm	NM ED 1998
	Annual[e]	0.02 ppm	
	3-hour[f]	0.50 ppm	
	24-hour[f]	0.14 ppm	
	Annual[f]	0.03 ppm	
New York	3-hour	0.25 ppm[g]; 0.50 ppm[h]	NY DEC 1998
	24-hour	0.10 ppm[g]; 0.14 ppm[h]	
	Annual	0.03 ppm	
North Dakota	1-hour	715 µg/m^3 (0.27 ppm)	ND SDHCL 1998
	24-hour	260 µg/m^3 (0.10 ppm)	
	Annual	60 µg/m^3 (0.02 ppm)	
Oregon	3-hour	0.02 ppm	OR DEQ 1998
	24-hour	0.10 ppm	
	Annual	0.50 ppm	
Washington	1-hour[h]	0.4 ppm	WA DE 1998
	1-hour[i]	0.25 ppm	
	24-hour	0.1 ppm	
	Annual	0.02 ppm	

TABLE 7-1. Regulations and Guidelines Applicable to Sulfur Dioxide (*continued*)

Agency	Description	Information	References
STATE (cont'd)			
Wyoming	3-hour	1300 μg/m^3 (0.50 ppm)	WY DEQ 1998
	24-hour	260 μg/m^3 (0.10 ppm)	
	Annual	60 μg/m^3 (0.02 ppm)	

[a]The Working Group on the Evaluation of Carcinogenic Risks to Humans concluded that this agent is not classifiable as to its carcinogenicity to humans. There is inadequate evidence in humans and limited evidence in animals.
[b]Not to be exceeded more than once per year.
[c]State regulations are not necessarily applied state-wide. For specific information as to the areas affected by the regulations, refer to the corresponding state's code of regulations. All states not listed have adopted the federal ambient air standards without modification. When designated, 1° indicates primary standards and 2° indicates secondary (more stringent) standards.
[d]Not to be exceeded more than eighteen times in any twelve consecutive months.
[e]For the state except on area within 3.5 miles of Chino Mines Company smelter furnace stack at Hurley.
[f]For area within 3.5 miles of Chino Mines Company smelter furnace stack at Hurley.
[g]99% of the 3 or 24-hour average concentrations shall not exceed this standard.
[h]Not to be exceeded more than once per year; [i]Not to be exceeded more than twice per week.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOT = Department of Transportation; DOT-IMO = Department of Transportation/International Maritime Organization; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FR = Federal Register; IARC = International Agency for Research on Cancer; NAAQS = National Ambient Air Quality Standard; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average; WHO = World Health Organization

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9. GLOSSARY

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

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 a 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.

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.

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.

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.

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.

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 occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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.

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

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

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

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

In Vivo-Occurring within the living organism.

Lethal Concentratioq($_{L0}$) (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentratioxq($_{50}$)(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($_{LO}$)(LO_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose($_{50}$)(LD_{50})-The dose of a chemical which 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 dose 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.

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

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

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

No-Observed-Adverse-Effect Level (NOAEL)-The dose of 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.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

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).

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 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 CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Specific Airway Resistance (SR_{aw}) In physiology, the resistance or opposition to flow of gases during ventilation due to obstruction or turbulent flow in the upper and lower airways.

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)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

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

Toxic Dose (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.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) 142 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 9994991, 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, summaryI 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, MREs 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 as much as a hundredfold 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, expert panel peer reviews, and agencywide 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, MRL,s in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Sulfur Dioxide
CAS Number: 7446-09-5
Date: November 1998
Profile Status: Third Draft Post-Public
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 25
Species: Human

Minimal Risk Level: 0.01 [ ] mg/kg/day [x] ppm

Reference: Sheppard et al. 1981. Exercise Increases Sulfur Dioxide-induced Bronchoconstriction in Asthmatic Subjects. Am Rev Respir Dis 123:486-491

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Two separate sets of studies on two separate groups of mild asthmatics were conducted. In the first set of studies, the effects of exercise on sulfur dioxide-induced bronchoconstriction was assessed in seven subjects (six men and one woman). The study design included an examination of the changes in specific airway resistance (SR_{aw}) produced by moderate exercise (10 minute duration) alone, inhalation of 0.10, 0.25, and 0.50 ppm sulfur dioxide alone, and the combination of exercise and sulfur dioxide. Subjects breathed sulfur dioxide and/or air from a mouthpiece.

In the second set of studies, a comparison was made between the bronchoconstriction produced by breathing sulfur dioxide during exercise and that produced by eucapnic hyperventilation with sulfur dioxide in six subjects (four men and two women). In one experiment, subjects were exposed to 1.0 ppm sulfur dioxide from a mouthpiece while exercising for 5 minutes. In another experiment, subjects were exposed to 1.0 ppm sulfur dioxide and instructed to hyperventilate. The pattern of hyperventilation approximated the pattern of the breathing of subjects during exercise. In addition, the effect of increased tidal volumes on the measurements of SR_{aw} after sulfur dioxide-induced bronchoconstriction was assessed in one subject since deep breathing may modify bronchoconstriction, and because hyperpnea occurs after exercise.

Effects noted in study and corresponding doses:

In the seven subjects with mild asthma, inhalation of 0.25 ppm sulfur dioxide during the performance of moderate exercise significantly increased SR_{aw}. Inhalation of 0.50 ppm during exercise significantly increased SR_{aw} in all seven subjects ($p<0.05$), and three developed wheezing and shortness of breath. During the corresponding period of exercise alone and during inhalation of 0.50 ppm at rest, SR_{aw} did not increase in any subject. After inhalation of 0.50 ppm of sulfur dioxide during exercise, ΔSR_{aw} (the difference between baseline specific airway resistance and specific airway resistance after inhalation of sulfur dioxide) was significantly greater than after exercise alone or inhalation of 0.50 ppm of sulfur dioxide at rest ($p<0.05$). Inhalation of 0.25 ppm sulfur dioxide during exercise significantly increased SR_{aw} in three of the seven subjects, and the increase in SR_{aw} for the group was significant ($p<0.05$). No subject developed wheezing or shortness of breath. During the corresponding period of exercise alone, SR_{aw} did not increase in any subject. In the two most responsive subjects, inhalation of 0.10 ppm significantly increased SR_{aw}, and there was a dose-response relationship to 0.10, 0.25, and 0.50 ppm in the 2 subjects. ΔSR_{aw} at 0.10 ppm was slight and

was approximately 2.5 L x cm H_20/L/s (units for ΔSR_{aw}). At 0.25 ppm, ΔSR_{aw} was approximately 5 L x cm H_20/L/s. At 0.5 ppm, the ΔSR_{aw} exceeded 15 L x cm H_20/L/s.

In the second set of studies, in all six subjects, inhalation of 1 ppm of sulfur dioxide dramatically increased SR_{aw}, both when it was delivered during exercise and during eucapnic hyperventilation (rapid, deep breathing to deplete arterial CO_2). In every case, the increase in SR_{aw} was accompanied by dyspnea and audible wheezing. The magnitude of the increase in SR_{aw} was the same when subjects inhaled sulfur dioxide while they exercised or while they performed eucapnic hyperventilation at the same minute ventilation.

The study authors concluded that moderate exercise increases the bronchomotor effect of sulfur dioxide in subjects with asthma so the concentrations as low as 0.10 ppm can cause sigificant bronchoconstriction. However, the ΔSR_{aw} at 0.10 ppm was slight. In addition, the authors stated that the concentrations studied are sometimes equaled or exceeded in polluted urban air, and that their findings support the contention that sulfur dioxide is at least partially responsible for the observed association between air pollution and increased morbidity from asthma.

Dose and endpoint used for MRL derivation:

[] NOAEL [X] minimal LOAEL

0.1 ppm, bronchoconstriction in exercising asthmatics

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

The uncertainty factor for human variability addresses varying sensitivity among asthmatics and possible increased sensitivity in children. There is concern of increased sensitivity in children but there is not sufficient data to confirm it.

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No, the doses provided are author-provided.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

None

Other additional studies or pertinent information which lend support to this MRL:

Lung function changes in asthmatics exposed by inhalation to sulfur dioxide have been reported by other investigators. In a chamber study of moderately exercising asthmatics, the concentration of sulfur dioxide required to produce an increase in airway resistance 100% greater than the response to clean air [designated as $PC(SO_2)$] has been determined (Horstman et al. 1986). Analysis of the cumulative percentage of subjects plotted as a function of $PC(SO_2)$ revealed that 25% of the subjects exhibited a $PC(SO_2)$ of 0.25 to 0.5 ppm sulfur dioxide. The study authors considered that the 25% of the mild asthmatics who were very sensitive to sulfur dioxide could possibly exhibit bronchoconstriction if they were to perform normal exercise routines in some highly industrialized areas of the United States. A dose-related increase in specific airway resistance

was seen in asthmatics following a 3 minute exposure (via mouthpiece) to ≥0.25 ppm sulfur dioxide (Myers et al. 1986a; Myers et al. 1986b).

Increases in specific airway resistance were observed in moderately exercising asthmatics exposed oronasally to 0.25 ppm sulfur dioxide for 5 minutes (Bethel et al. 1985). This study could have also been used to develop an MRL. An uncertainty factor of 30 would have been required (10 for the use of a LOAEL and 3 for human variability). Dividing the LOAEL of 0.25 ppm by an uncertainty factor of 30 results in an MRL of 0.01 ppm, a value consistent with the MRL derived from the Sheppard et al. (1981) study.
Some studies of asthmatics have reported a lack of significant lung function changes in asthmatics following exposures to 0.1-0.5 ppm (Jorres and Magnussen 1990; Koenig et al. 1990). Bronchoconstrictive responses to sulfur dioxide are highly variable among individual asthmatics (Horstman et al. 1986). In some studies asthmatics were preselected for sensitivity to sulfur dioxide and this may explain the range of sulfur dioxide-induced responses obtained by different investigators.

The dose level of 0.1 ppm sulfur dioxide can be considered a minimal LOAEL.

Agency Contact (Chemical Manager): Hana Pohl

Agency Review Date: 1° review:_____
2° review:_____

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1,2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (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 No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(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. When sufficient data

exists, 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) 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 2 " 18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (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 endpoint 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 8 of the profile.

(11) CEL A Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

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 intermediate and chronic 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, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a

NOAEL for the test species-rat. 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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 (ql*).

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

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

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 Data Needs section.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

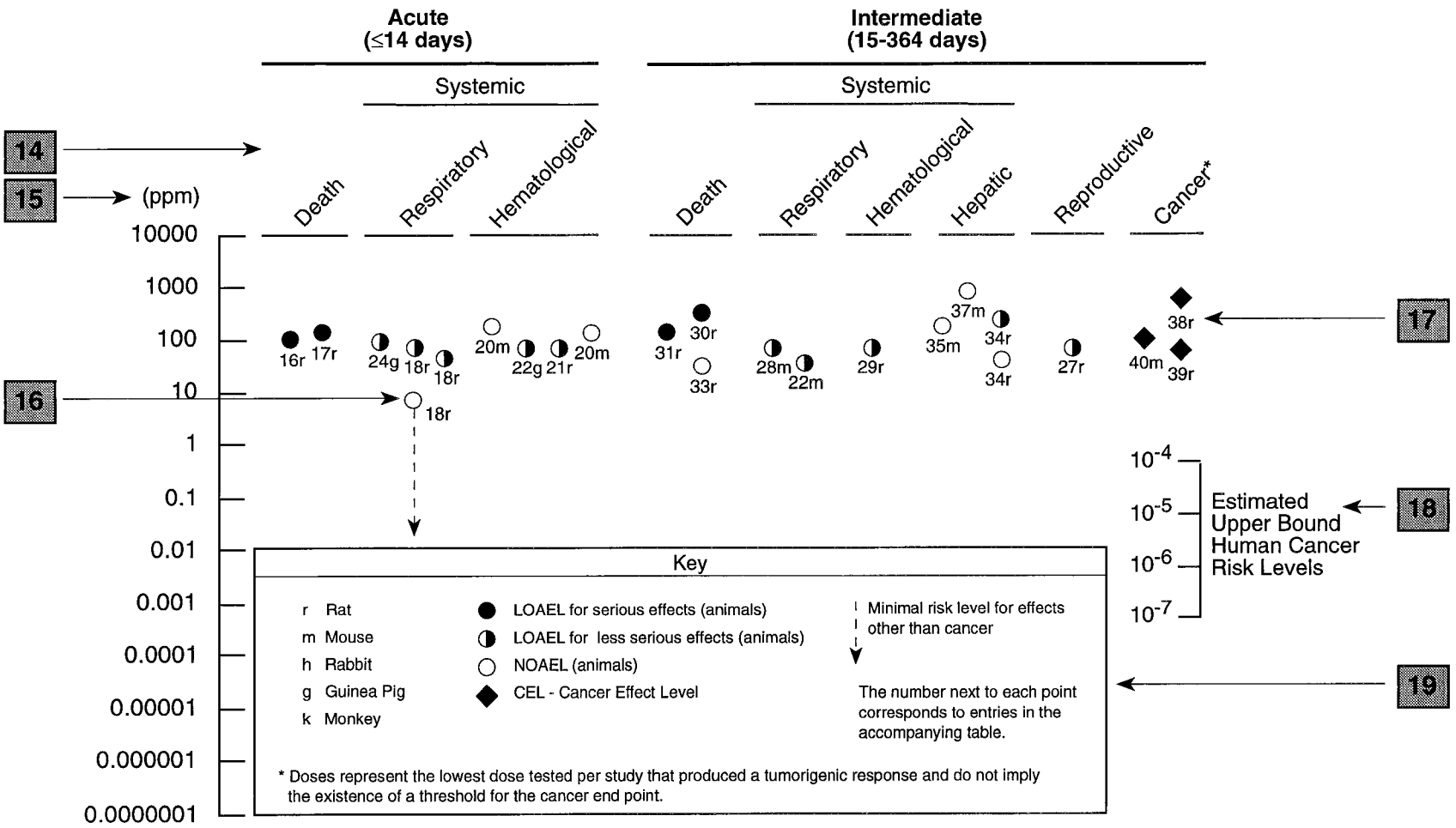
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11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

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

12 → [b] an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They 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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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 LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health

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IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration

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PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
S	sulfur
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
Tg	teragrams = 10^{12} grams
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram