Ingredient name: 1, 3 Butadiene

CAS No: 106-99-0; 9003-17-2; 68514-37-4

Datasheet No: 1327

TOXICOLOGICAL PROFILE FOR 1,3-BUTADIENE

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

September 2012

DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for 1,3-Butadiene, Draft for Public Comment was released in September 2009. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
Environmental Toxicology Branch (proposed)
1600 Clifton Road NE
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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 toxic substances each profile describes. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The profiles focus 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. A health effects summary describes the adequacy of information to determine a substance's health effects. ATSDR identifies data needs that are significant to protection of public health.

Each profile:

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

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

(C) Where appropriate, identifies 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 federal, state, and local health professionals; 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 also have 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.

Christopher J. Portier, Ph.D.
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*Legislative Background

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

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 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 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, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

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

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

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

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PEER REVIEW

A peer review panel was assembled for 1,3-butadiene. The panel consisted of the following members:

1. Sherif Abdel-Rahman, Ph.D., Department of Preventative Medicine and Community Health, University of Texas Medical Branch, Galveston, Texas

2. Genevieve Matanoski, M.D., Dr.PH, Bloomberg School of Public Health, The Johns Hopkins Univeristy, Baltimore, Maryland

3. Amir Sapkota, Ph.D., Maryland Institute for Applied Environmental Health, University of Maryland, School of Public Health, College Park, Maryland

These experts collectively have knowledge of 1,3-butadiene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

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LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about 1,3-butadiene and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. 1,3-Butadiene has been found in at least 13 of the 1,699 current or former NPL sites. Because not all NPL sites were tested for 1,3-butadiene, the number of sites where this chemical is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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 1,3-butadiene, many factors will determine whether you will 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 any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS 1,3-BUTADIENE?

Description	1,3-Butadiene is a colorless gas with a mild gasoline-like odor.
Uses	About 60% of 1,3-butadiene is used to make man-made rubber, which is then used mostly for car and truck tires. 1,3-Butadiene is also used to make certain types of plastics such as acrylics.

See Chapters 4 and 5 for more information on the sources, properties, and uses of 1,3-butadiene.

1.2 WHAT HAPPENS TO 1,3-BUTADIENE WHEN IT ENTERS THE ENVIRONMENT?

Sources	Large amounts of 1,3-butadiene are released into the air by industrial sources. Industrial releases to water and soil are relatively low. Automobile exhaust is a constant source of 1,3-butadiene release into the air. Other sources of 1,3-butadiene include cigarette smoke and the smoke of wood fires. Forest fires are considered to be a natural source of 1,3-butadiene in the air.
Break-down • **Air** • **Water and soil**	Half of the 1,3-butadiene in the air will likely be broken down in about 6 hours. 1,3-Butadiene that is spilled onto water or soil will likely evaporate quickly into the air based on its physical and chemical properties.

See Chapters 5 and 6 for more information on 1,3-butadiene in the environment.

1.3 HOW MIGHT I BE EXPOSED TO 1,3-BUTADIENE?

Air	The primary way you can be exposed to 1,3-butadiene is by breathing air containing it. Releases of 1,3-butadiene into the air occur from: • vehicle exhaust • tobacco smoke • wood burning • burning of rubber and plastic • forest fires • accidental or intentional release at manufacturing plants The average amount of 1,3-butadiene in the air is between 0.04 and 0.9 parts of 1,3-butadiene per billion parts of air (ppb) in cities and suburban areas.
Workplace air	Workers in the production of rubber, plastics, and resins are likely exposed to higher levels of 1,3-butadiene.

Food and drinking water	1,3-Butadiene has been measured at very low levels in plastic or rubber of food containers, but it has not been found often in food samples. Exposure to 1,3-butadiene through ingestion of food and drinking water is expected to be very low compared to exposure through breathing contaminated air.
Gasoline	People may be exposed to small amounts of 1,3-butadiene if gasoline gets on their skin or by breathing air that contains gasoline fumes.

1.4 HOW CAN 1,3-BUTADIENE ENTER AND LEAVE MY BODY?

Enter your body	1,3-Butadiene in air can be absorbed from the lungs and enter the blood stream.
Leave your body	1,3-Butadiene is broken down to other chemicals in the liver. About half of inhaled 1,3-butadiene is broken down and exhaled, while most of the remaining chemical is broken down and excreted in the urine. 1,3-Butadiene typically leaves the body by 10 hours.

For more information on how 1,3-butadiene enters and leaves the body, see Chapter 3.

1.5 HOW CAN 1,3-BUTADIENE AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Noncancer	In laboratory animals, 1,3-butadiene causes inflammation of nasal tissues, changes to lung, heart, and reproductive tissues, neurological effects, and blood changes.

Cancer	Studies of workers exposed to 1,3-butadiene suggest that workers may have an increased risk for cancers of the blood and lymphatic system. Laboratory animals have developed cancer in multiple body tissues after exposure to 1,3-butadiene for 13 weeks or longer. Animals appear to be most sensitive to blood and lymphatic system cancers. The International Agency for Research on Cancer (IARC), National Toxicology Program (NTP), and EPA all classify 1,3-butadiene as a human carcinogen.

1.6 HOW CAN 1,3-BUTADIENE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	It is likely that children would show the same health effects as adults. We do not know whether children are more sensitive to the effects of 1,3-butadiene.
Birth defects	We do not know whether 1,3-butadiene causes birth defects in people. Some studies have found decreases in fetal weight and skeletal defects in laboratory animals exposed to 1,3-butadiene.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO 1,3-BUTADIENE?

Wood burning	Take precautions to minimize the amount of smoke released into the home during wood burning.
Vehicle engines	Make sure vehicle engines are turned off when in an enclosed space such as a garage.
Vehicle traffic	Minimize time spent near areas of heavy vehicle traffic and avoid living very close to busy roads.
Tobacco smoke	Families can reduce exposure to 1,3-butadiene by avoiding tobacco smoke, particularly indoors.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,3-BUTADIENE?

Development of blood tests	We currently have no reliable medical test to determine if someone has been exposed to 1,3-butadiene. However, scientists are working on tests to show if 1,3-butadiene attaches to compounds in the blood, such as proteins or deoxyribonucleic acid (DNA).

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

Regulations and recommendations can be expressed as "not-to-exceed" levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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

Some regulations and recommendations for 1,3-butadiene include the following:

Levels in breathing air set by EPA	EPA has set a reference concentration in breathing air of 0.9 ppb for 1,3-butadiene.
Levels in drinking water set by EPA	EPA has not set levels in drinking water for 1,3-butadiene.
Levels in workplace air set by OSHA	OSHA set a legal limit of 1 ppm for 1,3-butadiene in air averaged over an 8-hour work day.

1.10 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 contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,3-BUTADIENE IN THE UNITED STATES

1,3-Butadiene is a highly volatile gas that is used in the production of synthetic rubber; the major end use of the synthetic rubber is automobile tires. 1,3-Butadiene is also used for the production of high impact polystyrene and acrylonitrile-butadiene-styrene (ABS) resin plastics The predominant source of 1,3-butadiene in the atmosphere is industrial releases, which can occur during manufacturing, use, transport, and storage of the chemical. Automobile exhaust is a constant source of low levels of 1,3-butadiene release to the atmosphere. Minor sources of 1,3-butadiene in the atmosphere include cigarette smoke, wood burning (including forest fires), and the burning of rubber and plastics. In the atmosphere, 1,3-butadiene is expected to undergo photo-initiated destruction with a half-life of approximately 6 hours. Relatively low levels of 1,3-butadiene are released to water and soil. 1,3-Butadiene in water or soil is expected to rapidly evaporate to the atmosphere.

Inhalation is the predominant route of exposure for the general population. Mean concentrations of 1,3-butadiene in the air in cities and suburban areas ranges from 0.1 to 2 $\mu g/m^3$ (0.04–1 ppb); the average background concentration of 0.13 $\mu g/m^3$ (0.59 ppb) has been estimated. Higher atmospheric concentrations have been measured in areas near oil refineries, chemical manufacturing plants, and plastic and rubber factories where 1,3-butadiene is manufactured or used; concentrations as high as 40 $\mu g/m^3$ (18 ppb) have been measured near industrial sites. Within the general population, smokers (and individuals exposed to secondhand smoke) and individuals inhaling smoke from wood fires are likely to be exposed to higher levels of 1,3-butadiene. Workers involved in the production of rubber, plastics, and resins are most likely to receive the largest exposures. No data are available to quantify general population exposure to 1,3-butadiene by other routes of exposure, but it is expected to be very low compared to breathing contaminated air. Low levels of 1,3-butadiene have been detected in U.S. drinking water supplies; however, specific quantitative data were not located. 1,3-Butadiene has also been measured at very low levels in the plastic or rubber of food containers and has been found in a few food samples.

Several biomarkers of exposure have been identified for 1,3-butadiene; these include 1,3-butadiene urinary metabolites, M1 and M2, and three hemoglobin adducts, *N*-(2-hydroxy-3-butenyl)valine (MHB-Val), *N*-(2,3,4-trihydroxybutyl)valine (THB-Val), and *N*,*N*-(2,3-dihyroxy-1,4-butadyl)valine (*pyr*-Val), which are surrogate biomarkers for the 1,3-butadiene metabolites 1,2 epoxy-3-butene (EB),

1,2-dihydroxy-3,4-epoxybutane (EBD), and 1,2:3,4-diepoxybutane (DEB), respectively. In workers, the levels of urinary metabolites and hemoglobin adducts have been shown to correlate with 1,3-butadiene exposure levels. However, background levels for the general population have not been established for these biomarkers of exposure.

2.2 SUMMARY OF HEALTH EFFECTS

The available data for 1,3-butadiene exposure and toxicity in humans and animals are limited to inhalation exposures; the effects from significant oral or dermal exposures are not known. Information on the toxicity of 1,3-butadiene in humans comes from case reports and epidemiology studies that primarily focused on the potential carcinogenicity of 1,3-butadiene. Slight eye irritation and difficulty in focusing on instrument scales were reported by two men exposed to 2,000 or 4,000 ppm 1,3-butadiene for 6–7 hours; however, this was not reported when the two men were exposed to 8,000 ppm for 8 hours. Psychomotor tests conducted in these subjects did not find alterations at 2,000–8,000 ppm. Numerous epidemiological studies of multiple occupational cohorts, including one encompassing 15,000 workers, have associated a higher incidence of hemato-lymphopoietic cancer mortality among exposed workers. Although most of these workers were co-exposed to other organic compounds, including styrene, benzene, and dithiocarbamates, multivariate analysis suggested that the estimates of 1,3-butadiene exposure provided the best correlation with the rates of lympho-hematopoietic cancers.

Numerous target organs for 1,3-butadiene toxicity have been identified in well-conducted laboratory studies ranging from single episode to lifetime exposures. Observed effects include death, neurological dysfunction, reproductive and developmental effects, hematological and lymphoreticular effects, and cancer. Evaluation of the relevance of adverse health effects observed in laboratory animals to human health is encumbered by large species differences in the metabolism of 1,3-butadiene. The metabolism of 1,3-butadiene in humans and laboratory animals involves the same enzymatic pathways; however, there are notable quantitative differences in the production and detoxification of several reactive metabolites, particularly, EB, DEB, and EBD; see Sections 3.4.2 and 3.5.3 for more information on species differences. Mice, the most sensitive species, are more efficient at converting 1,3-butadiene to EB and converting EB to DEB. Using *pyr*-Val hemoglobin adduct levels as a biomarker for blood DEB levels, an exposure to approximately 1 ppm 1,3-butadiene resulted in mouse DEB levels that were 50 times higher than rats and 1,000 times higher than humans. Although the mode of action has not been elucidated for all toxic end points, there are strong data to support the reactive metabolites as the causative agents for the ovarian atrophy, cancer, and genotoxic effects observed in laboratory animals. Without information on

the mode of action, particularly the causative agent, the reader should use caution in evaluating the relevance of the animal data presented in this section to human health.

Lesions of the respiratory tract (olfactory tissues and lungs), liver, kidney, stomach, and eyes have been seen in mice exposed to ≥200 ppm for intermediate durations, but these lesions are typically epithelial or endothelial hyperplasias and are precancerous in nature. Non-neoplastic lesions of the liver (necrosis) in rats and kidney (renal nephrosis) in mice occurred following intermediate-duration exposure to 625 or 8,000 ppm, respectively.

Although no biologically relevant alterations in hematological parameters have been observed in 1,3-butadiene workers, changes in the blood and lymphoid tissues are common observations in rodents exposed for intermediate and chronic durations. Decreases in red blood cell counts and hemoglobin concentration occurred at 65 ppm in mice, progressing to macrocytic megaloblastic anemia from exposures of 200 ppm. These effects are likely associated with observed changes in normal bone marrow function, as indicated by reduced circulation of erythrocytes and leukocytes, and increased proliferative activity with no associated change in bone marrow cellularity. Lymphoreticular toxicity in mice was indicated by significant changes in thymus weight and lesions in lymphoid organs following intermediate-duration exposures to 625–1,250 ppm in mice. A reversible suppression of cytotoxic T-lymphocyte generation to mastocytoma cells and a depression of spleen cellularity were observed at these exposures. The changes in spleen and thymus weights, lymphocytic differentiation, and appearance of lymphoid lesions comport with the onset of lymphoma in mice after chronic exposure to 1,3-butadiene.

Reproductive and developmental effects are the most sensitive non-cancer effects observed in rodents. Wavy ribs and skeletal abnormalities occurred in offspring of rats exposed to 1,000–8,000 ppm during gestation days (GDs) 6–15. In mice, exposure of pregnant dams to 40 ppm on GDs 6–15 resulted in a 5% decrease in fetal body weight among male mice. Exposure of mice to ≥200 ppm resulted in ≥19% reductions in fetal weight. A possible dominant lethal effect was observed in mice in which increased fetal deaths occurred from exposure to 200 ppm. The lowest lowest-observed-adverse-effect level (LOAEL) identified for intermediate-duration exposures was 12.5 ppm in male mice mated with unexposed females, resulting in increased late fetal death, exencephaly, and skull abnormalities of fetuses. Serious lesions of reproductive tissues in male and female mice have arisen from intermediate- and chronic-duration exposures. Ovarian atrophy, including complete loss of oocytes, follicles, and corpora lutea, occurred in mice exposed to 200 ppm for 9 months and as low as 6.25 ppm for 2 years. Male mice

were somewhat less sensitive, with testicular atrophy observed after 15-month exposures to 625 ppm 1,3-butadiene.

The consistent carcinogenic responses in rodent bioassays support the associations derived in epidemiological studies between hemato-lymphopoietic cancer and 1,3-butadiene exposure. In rats, 2-year exposure to 1,000 or 8,000 ppm resulted in increased incidences of tumors of the testes, pancreas, uterus, mammary gland, Zymbal gland, and thyroid. In mice, exposure to 200 ppm for 40 weeks resulted in increased tumor incidences of lymphopoietic system, heart, lung, stomach, liver, and eye. These same tumors developed in mice in as little as 13 weeks after exposure to 625 ppm. Chronic exposure of mice to concentrations of 20 ppm (males) and 6.25 ppm (females) of 1,3-butadiene resulted in increased tumor development in the lymphopoietic system, heart, lung, stomach, liver, eye, mammary glands, and ovaries.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

The toxicity of 1,3-butadiene following inhalation exposure has been examined in epidemiology studies, intermediate- and chronic-duration studies in rats and mice, reproductive toxicity studies in mice, and developmental toxicity studies in rats and mice. The epidemiological studies have primarily focused on carcinogenicity and have found increases in lympho-hematopoitic cancers. Observed effects found in animal studies include neurological dysfunction, reproductive and developmental effects, hematological and lymphoreticular effects, and cancer. Acute exposures have resulted in fetal effects (decreased growth and skeletal defects) (DOE/NTP 1987b; Irvine 1981) and reproductive effects (increased intrauterine death following male-only exposure) (DOE 1988b). Intermediate-duration exposures in mice resulted in precancerous lesions of the respiratory tract (olfactory tissues and lungs), liver, kidney, stomach, and eyes (NTP 1984, 1993). Non-neoplastic lesions of the liver (necrosis) in rats and kidney (renal nephrosis) in mice occurred following intermediate-duration inhalation exposure. In mice, intermediate-duration inhalation exposure also resulted in decreases in red blood cell counts and hemoglobin concentration, progressing to macrocytic megaloblastic anemia (NTP 1993), decreases in spleen and thymus weight (NTP 1993), and depressed splenic cellularity (Thurmond et al. 1986). Chronic-duration inhalation exposure studies identified a number of targets of toxicity in mice including, bone marrow, lungs, heart, forestomach, Harderian gland, testes, ovaries, and uterus (NTP 1984, 1993); neoplastic lesions were also observed in a number of tissues. In rats, chronic exposure resulted in histological alterations in the lungs and increased severity of nephropathy (Owen et al. 1987).

Comparison of rat and mouse data identifies large differences in sensitivity to 1,3-butadiene, which are due to metabolic differences between species. As discussed in Sections 3.4.2 and 3.5.3, quantitative differences between humans, rats, and mice in the rate of formation of reactive metabolites, particularly EB and DEB have been found. These differences result in higher tissue levels of reactive metabolites in rodents than in humans (Bond et al. 1993; Csanády et al. 1992; Dahl et al. 1991; Filser et al. 2001, 2007, 2010; Henderson et al. 1996, 2001; Himmelstein et al. 1997; Kirman et al. 2010a; Krause and Elfarra 1997; Schmidt and Loeser 1985; Thornton-Manning et al. 1995b). Following inhalation exposure to 1,3-butadiene, blood EB levels were 2–8 times higher in mice as compared to rats (Filser et al. 2007) and the maximum butadiene-diol levels were 4 times higher in mice than rats (Filser et al. 2007). The DEB levels were >100-fold higher in mice as compared to rats (Filser et al. 2007). At a similar exposure level (1 ppm), mice produce approximately 1,000 times as much DEB as humans, as measured using *pyr*-Val hemoglogin adduct as a biomarker and 50 times as much DEB as rats (Swenberg et al. 2011).

The Agency usually considers humans more sensitive than animals and makes an adjustment to the point of departure to account for species differences when deriving an MRL from an animal study. If possible, chemical-specific data, such as physiologically based pharmacokinetic (PBPK) modeling, is used to account for toxicokinetic differences between species. Although PBPK models for 1,3-butadiene have been developed in rodents (Johanson and Filser 1993; Kohn and Melnick 1993, 1996, 2000) and a preliminary model has been developed in humans (Brochot et al. 2007), the models are limited in their ability to predict internal doses for key metabolites (Kirman and Grant 2012). An alternative to using PBPK models would be to use a biomarker of exposure to reactive metabolites. Several biomarkers of exposure have been identified for reactive 1,3-butadiene metabolites including MHB-Val hemoglobin adducts, THB-Val hemoglobin adducts, and *pyr*-Val hemoglobin adducts, which have been shown to be good surrogate biomarkers for EB, EBD, and DEB, respectively (Georgieva et al. 2010; Slikker et al. 2004). However, there are limited mechanistic data that would allow identification of the 1,3-butadiene metabolite(s) (or parent compound) that is responsible for the non-neoplastic effects, with the exception of ovarian atrophy observed in mice, which is likely due to DEB.

In the absence of chemical-specific data, the Agency generally applies an uncertainty factor of 10 to account for interspecies differences in toxicokinetic and toxicodynamic properties. However, the toxicokinetic data for 1,3-butadiene indicate that mice are many-fold more sensitive than humans. Thus, the Agency can only use an uncertainty factor of 1 (or not apply an uncertainty factor [UF]), which in the case of 1,3-butadiene, may cause the MRL to overestimate the risk to humans. Therefore, in this instance,

the Agency has elected to not derive inhalation MRLs for 1,3-butadiene. Brief discussions of the available literature for each duration period are presented below.

Acute-Duration Inhalation MRL. Death and neurological effects have been observed in rats, mice, and rabbits exposed to 8,000–250,000 ppm from <1 to 4 hours (Carpenter et al. 1944; Shugaev 1969). Studies examining nonlethal effects were limited to three developmental toxicity studies and a reproductive toxicity study. Significant increases in the occurrence of major skeletal defects, predominantly wavy ribs, were observed in the offspring of Sprague-Dawley rats exposed to 1,000 or 8,000 ppm 1,3-butadiene 6 hours/day on GDs 6–15 (Irvine 1981). Other non-concentration-related effects included an increase in minor skeletal defects at 200 ppm, but not at higher concentrations, and increases in the occurrence of minor external/visceral defects at 1,000 ppm, but not at 8,000 ppm. The study also found decreases in fetal growth (body weight and crown-rump length) at 8,000 ppm and decreases in maternal weight gain at ≥200 ppm; at 8,000 ppm, maternal body weight gain was 45% lower than controls. The investigators noted that the increase in the occurrence of wavy ribs was likely secondary to the decrease in maternal weight gain. In a second rat developmental toxicity study, no developmental effects (including alterations in occurrence of skeletal defects, fetal body weight, or maternal body weight) were observed in Sprague-Dawley rats exposed to 40–1,000 ppm 6 hours/day on GDs 6–15 (DOE/NTP 1987a). In a mouse developmental toxicity study, decreases in fetal body weight were observed in the offspring of CD-1 mice exposed to ≥40 ppm 6 hours/day on GDs 6–15 (DOE/NTP 1987b). The male fetal body weights were 5, 18, and 23% lower than controls and no significant alterations in female body weight were observed; interpretation of these results is limited by the lack of statistical adjustment for litter size. In the reproductive toxicity study, the mating of male CD-1 mice exposed to ≥200 ppm 6 hours/day for 5 days with unexposed females resulted in significant increases in dams with two or more intrauterine deaths (DOE/NTP 1988b). This effect was only observed when the mating occurred 1 week post-exposure, suggesting that the mature spermatozoa and/or spermatids were the targets.

The limited available data on the toxicity of 1,3-butadiene following acute-duration inhalation exposure suggest that mice are more sensitive than rats for developmental effects. Exposures to 1,3-butadiene has resulted in decreases in fetal body weights in mice at ≥40 ppm (DOE/NTP 1987b) and rats at ≥200 ppm (Irvine 1981), dominant lethal effects in mice at ≥200 ppm (DOE/NTP 1988b), and increases in skeletal malformations in rat fetuses at ≥1,000 ppm (Irvine 1981). The no-observed-adverse-effect levels (NOAELs) were 40 ppm for dominant lethal effects in mice and 200 ppm for skeletal defects in rats. As noted previously, the Agency has elected to not derive an acute-duration inhalation MRL for 1,3-butadiene due to the large species differences in the metabolism of 1,3-butadiene and the lack of

chemical-specific data to adjust for these differences, which may result in the MRL overestimating the risk to humans.

Intermediate-Duration Inhalation MRL. Intermediate-duration exposures resulted in death in mice exposed to 5,000 ppm, 6 hours/day for 5 weeks (NTP 1984) and 200 ppm, 6 hours/day for 40 weeks (NTP 1993). No systemic effects were seen in rats or mice exposed to 8,000 ppm, 6 hours/day for 13–14 weeks, with the exception of a 13% body weight reduction in mice exposed to 2,500 ppm (NTP 1984). Exposure of mice to 625 ppm, 6 hours/day for 40 weeks resulted in pre-cancerous hyperplasia of the respiratory and gastrointestinal systems (epithelial hyperplasia), as well as a 19% reduction in thymus weight. Multi-site cancer was observed in mice after 13–52 weeks of exposure to 200 ppm for 6 hours/day (NTP 1993). Hematological effects included decreased erythrocyte counts, hemoglobin concentration, and red blood cell volume in mice at 62.5 ppm and macrocytic megaloblastic anemia at 200 ppm, administered 6 hours/day for 40 weeks (NTP 1993). Reproductive effects in mice were the most sensitive effects observed, with ovarian atrophy occurring at exposures of 200 ppm, 6 hours/day for 40 weeks (NTP 1993). The most sensitive developmental effects observed were exencephalies, skull abnormalities, and late fetal death in the offspring of unexposed female mice mated with male mice exposed to 12.5 ppm for 10 weeks (Anderson et al. 1996).

The Agency has elected to not derive an intermediate-duration inhalation MRL for 1,3-butadiene due to the large species differences in the metabolism of 1,3-butadiene and the lack of chemical-specific data to adjust for these differences, which may result in the MRL overestimating the risk to humans.

Chronic-Duration Inhalation MRL. Chronic-duration exposures resulted in increased mortality in rats and mice exposed to 8,000 or 20 ppm, 6 hours/day for 2 years. Rats exposed to 8,000 ppm, 6 hours/day for 2 years exhibited increased lung weight and metaplasia and kidney nephrosis (Owen and Glaister 1990; Owen et al. 1987). In mice, exposure to 1,250 ppm for 65 weeks resulted in nasal olfactory epithelial atrophy in mice (NTP 1984). Hepatic necrosis, forestomach epithelial hyperplasia, megaloblastic anemia, and endothelial hyperplasia of the heart were observed in mice exposed to 625 ppm (6 hours/day, 5 days/week) for 61–65 weeks (NTP 1984, 1993); testicular atrophy and preputial gland hyperplasia were observed in mice exposed to 625 ppm for 2 years (NTP 1993). Ovarian atrophy was observed in mice exposed to 62.5 ppm for 65 weeks or 6.25 ppm for 2 years (NTP 1993); complete destruction of oocytes, follicles, and corpora lutea was also observed. Alveolar epithelial hyperplasia was observed in mice following a 2-year exposure to 6.25 ppm (NTP 1993). In addition to the noncancerous effects, mammary gland tumors developed in rats exposed to 1,000 ppm, 6 hours/day for 2 years (Owen

and Glaister 1990; Owen et al. 1987), while multi-site cancer was observed in mice at 625 ppm, 6 hours/day for 61 weeks (NTP, 1984) and lung cancer occurred in mice following exposure to 6.25 ppm, 6 hours/day for 2 years (NTP 1993).

Considerable species differences were observed in the chronic-duration studies in terms of observed effects and sensitivity. The lowest LOAEL in rats is 8,000 ppm for lung and kidney effects and the lowest LOAEL in mice is 6.25 ppm for ovarian and lung effects. Renal effects have not been observed in mice exposed to up to 625 ppm for 2 years (NTP 1993) and ovarian effects were not observed in rats exposed to concentrations as high as 8,000 ppm for 2 years (Owen et al. 1987). The differences in sensitivity and possibly critical targets are most likely related to species differences in 1,3-butadiene metabolism. As noted previously, mice produce substantially more DEB than rats; one study (Thornton-Manning et al. 1995b) found that peak tissue levels of DEB were 40–160-fold greater in mice than rats. A comparison of blood DEB levels estimated from *pyr*-Val hemoglobin adduct levels found that at similar exposure levels (approximately 1 ppm), mouse DEB levels were 50 times higher than in rats and 1,000 times higher than in humans (Swenberg et al. 2011). In the absence of human data for noncarcinogenic effects following chronic exposure, the species differences in metabolism necessitate estimating human equivalent concentrations for each end point and comparing these values in order to identify the most likely critical target in humans. The available data provide strong evidence that the 1,3-butadiene metabolite, DEB, is the causative agent of the ovarian atrophy observed in mice (Doerr et al. 1996). Mechanistic data that could be used to identify relevant internal dose metrics for other sensitive end points in rats and mice were not identified, which precludes a comparison of human equivalent concentrations for each sensitive target. Thus, the Agency has elected to not derive a chronic-duration inhalation MRL for 1,3-butadiene; the lack of chemical-specific data to adjust for the large species differences in metabolism may result in the MRL overestimating the risk to humans.

Although ATSDR considers that the lack of data that can be used to evaluate the most sensitive target of chronic toxicity in humans precludes derivation of a chronic-duration inhalation MRL, the U.S. EPA (IRIS 2012), the Texas Commission on Environmental Quality (TCEQ) (Grant et al. 2010), and Kirman and Grant (2012) have derived chronic risk assessment values based on ovarian atrophy in mice. These three approaches share several commonalities, but also have several differences. All three approaches use a time-to-response benchmark dose (BMD) model; EPA and TCEQ used incidence data from the National Toxicology Program (NTP 1993) chronic mouse study and Kirman and Grant (2012) used incidence data from intermediate- and chronic-duration rat and mouse studies. The EPA approach did not make any adjustments for chemical-specific differences in metabolism. TCEQ derived chemical-specific

uncertainty factors to account for species differences in DEB formation, whereas Kirman and Grant (2012) ran the BMD modeling using an internal dose metric for DEB. A summary of these risk assessment values are presented in Table 2-1 and a more detailed discussion of the three approaches follows.

EPA (IRIS 2012). In 2002, EPA derived a reference concentration (RfC) of 0.0009 ppm based on a $BMCL_{10}$ of 0.88 ppm using the concentration-response data for ovarian atrophy in mice exposed to 1,3-butadiene for 2 years (NTP 1993) and an uncertainty factor of 1,000 (3 for interspecies extrapolation with dosimetric adjustments, 10 for intraspecies variability, 3 for incomplete database, and 10 for extrapolation to a level below the 10% effect level). The BMD modeling used the Weibull time-to-response model and incorporated the incidence data from the interim and final sacrifices; the data were modeled to include extra risk only until age 50 years. Human equivalent concentrations were calculated by adjusting the $BMCL_{10}$ for intermittent exposure (6 hours/day, 5 days/week) and multiplying the adjusted $BMCL_{10}$ by an RGDR (ratio of blood:gas partition coefficients) of 1.

Texas Commission on Environmental Quality (Grant et al. 2010). The TCEQ (Grant et al. 2010) derived a chronic reference value of 0.0154 ppm based on a $BMCL_{05}$ of 0.462 ppm for ovarian atrophy in mice (NTP 1993) and a total uncertainty factor of 30. Similar to EPA, the Weibull time-to-response model was used for BMD analysis of the ovarian atrophy incidence data for mice exposed to 1,3-butadiene for 2 years (9- and 15-month interim sacrifice data were also included in the model). The component uncertainty factors were 1 for animal to human extrapolation, 10 for intraspecies variability, and 3 for database deficiencies (lack of a multigenerational reproductive study). Both the intraspecies and the interspecies uncertainty factors were divided into toxicokinetic and toxicodynamic components. For the intraspecies uncertainty factor, a default value of 3 was used to account for toxicodynamic factors because data are lacking on the key sequence of events and how DEB interacts in different subpopulations to produce ovarian atrophy; a toxicokinetic factor of 3 was used because metabolic genetic polymorphisms may account for differences in susceptibility of 2–3.5-fold in humans. For the interspecies uncertainty factor, 3 was used for toxicodynamic differences because data are not available on possible differences on how DEB would react in different species to produce ovarian atrophy; a toxicokinetic factor of 0.3 was selected to account for species differences in 1,3-butadiene metabolism. The basis of this 0.3 factor was: (1) a comparison of the levels of DEB-specific hemoglobin adduct (*pyr*-Val adduct) formation in mice and humans; (2) a comparison of total 1,3-butadiene metabolite levels in the blood; and (3) comparisons of DEB blood concentrations, DEB tissue levels, and blood area-under-

Table 2-1. Summary of Available Chronic Risk Assessment Values for 1,3-Butadiene

Source	Source of data for benchmark analysis	POD	UF (UF_L, UF_A, UF_H, UF_{DB})	Issues and considerations
EPA (IRIS 2012)	2-Year mouse study (including interim sacrifices)	$BMCL_{10}$: 0.88 ppm	1,000 (10, 3, 10, 3)	The RfC does not have a chemical-specific adjustment for the increased production of DEB (reactive metabolite) in mice, as compared to humans. Does not take into consideration that ovarian atrophy may not be the most sensitive target in humans and that effects due to exposure to other reactive metabolites may occur at lower doses.
TCEQ (Grant et al. 2010)	2-Year mouse study (including interim sacrifices)	$BMCL_{05}$: 0.462 ppm	30 (NA, 1, 10, 3)	Accounts for species differences by quantifying toxicokinetic differences between mice and humans and selecting the low end of the range as an uncertainty factor to account for interspecies toxicokinetic differences. Does not take into consideration that ovarian atrophy may not be the most sensitive end point in humans and that effects due to exposure to other reactive metabolites may occur at lower doses.
Kirman and Grant 2012	Intermediate and chronic rat and mouse studies	$BMCL_{01}$: 1.5 ppm	10 (NA, 3, 1, 3)	Accounts for species differences by including rat incidence data in BMD model and using *pyr*-Val hemoglobin adduct levels as a biomarker of DEB levels. Does not take into consideration that ovarian atrophy may not be the most sensitive end point in humans and that effects due to exposure to other reactive metabolites may occur at lower doses.

BMCL = 95% lower confidence limit of the benchmark concentration; BMD = benchmark dose;
DEB = 1,2:3,4-diepoxybutane; LOAEL = lowest-observed-adverse-effect level; NA = not applicable;
NOAEL = no-observed-adverse-effect level; POD = point of departure; RfC = reference concentration;
UF = uncertainty factor: UF_L = extrapolation from NOAEL to LOAEL; UF_A = extrapolation from animals to humans;
UF_H = human variability; UF_{DB} = database limitations

the-curve levels in rats and mice; these comparisons resulted in a range of toxicokinetic uncertainty factors of 0.01–0.2 and the value of 0.3 was selected.

Kirman and Grant (2012). Kirman and Grant (2012) based their RfC of 0.2 ppm on a $BMCL_{01}$ of 1.5 ppm for ovarian atrophy and an uncertainty factor of 10 (3 for extrapolation from animals to humans and 3 for database deficiencies [lack of a multigenerational study and lack of dose-response data for follicle depletion]). A multi-stage Weibull time-to-response BMD model was applied to the combined dose-response data for ovarian atrophy in mice exposed for 2 years (including 40- and 65-week interim sacrifices (NTP 1993), mice exposed for 61 weeks (NTP 1984), mice exposed for 13 weeks (Bevan et al. 1996), rats exposed for 2 years (Owen et al. 1987), and rats exposed for 13 weeks (Bevan et al. 1996). To account for species differences in the metabolism of 1,3-butadiene, the BMD model was run using blood DEB levels as the internal dose metric. Blood DEB levels were estimated using a multistep process that used *pyr*-Val adduct burden as a biomarker for DEB levels. *Pyr*-Val adduct burdens were estimated using data on *pyr*-Val adduct efficiency (amount of adducts formed per ppm of 1,3-butadiene in air) in rats and mice as a function of 1,3-butadiene exposure concentration following a 4-week exposure (6 hours/day, 5 days/week). The estimated *pyr*-Val adduct burden were then used to calculate blood DEB concentrations using species-specific rate constants for the reaction of DEB with the terminal valine of hemoglobin and erythrocyte lifespan. For the time-to-response model, the exposure duration of interest was set equal to the window of susceptibility for ovotoxicity. Since the window of susceptibility is dependent on the number of follicles present at birth, the model was run for three scenarios: an average number of follicles at birth, the lower bound of central tendency for number of follicles, and the upper bound of the central tendency for the number of follicles; the range of susceptibility for depletion of follicle reserves for 95% of the population ranges from 8.5 higher and 8.5 lower than the average individual. The BMD model also included a 3-fold shift to account for toxicokinetic variation among humans. Since the model accounts for toxicokinetic and toxicodynamic differences in humans, no additional uncertainty factors were added to account for human variability.

Oral MRLs

There are no data available for effects in humans or animals exposed orally to 1,3-butadiene. For this reason, no acute-, intermediate-, or chronic-duration oral MRLs could be derived.

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,3-butadiene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,3-butadiene are indicated in Table 3-1 and Figure 3-1. Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 1,000,000 (10^{-4} to 10^{-6}), as developed by EPA.

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

3.2.1 Inhalation Exposure

3.2.1.1 Death

Information on the lethality of 1,3-butadiene in humans is limited. A number of occupational exposure studies have examined mortality ratios in 1,3-butadiene workers, the results of these studies are discussed in subsequent sections on the primary effects.

No deaths were seen in B6C3F1 mice exposed to ≤8,000 ppm 1,3-butadiene 6 hours/day, 5 days/week, for 2 weeks (NTP 1984). The majority of rabbits died when exposed to 250,000 ppm 1,3-butadiene for an average of 23 minutes (Carpenter et al. 1944). The LC_{50} values calculated for mice and rats exposed for 2 and 4 hours, respectively, was 122,000 and 129,000 ppm, respectively (Shugaev 1969).

Intermediate-duration exposures produced no deaths in rats exposed for 6 hours/day, 5/days/week, for 13 weeks to 8,000 ppm (Crouch et al. 1979), or in rats, guinea pigs, rabbits, and dogs during 8 months of exposure to 6,700 ppm (Carpenter et al. 1944). Increased mortality was seen in mice exposed to 5,000 ppm, but not 2,500 ppm, for 6 hours/day, 5 days/week, for 14 weeks (NTP 1984). The lowest

intermediate-duration exposure resulting in death was observed in mice receiving 200 ppm for 6-hours/day, 5 days/week, for 40 weeks (NTP 1993), ostensibly from the early development of neoplasms.

During chronic exposure to 625 and 1,250 ppm of 1,3-butadiene for 61 weeks, significantly increased mortality, primarily due to cancer, was found in B6C3F1 mice (NTP 1984). Similar results were obtained in another study using a much lower concentration (20 ppm) (NTP 1993). Exposure of rats to 8,000 ppm 1,3-butadiene resulted in statistically significant increased mortality from cancer when compared with controls (Owen et al. 1987). The LC_{50} values and all reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

Respiratory Effects. Workers exposed to 1,3-butadiene gas during the manufacture of rubber complained of irritation of the eyes, nasal passages, throat, and lungs (Wilson 1944). In some, coughing, fatigue, and drowsiness developed. All symptoms disappeared on removal from the gas. The associated exposure levels were not reported.

No effects in respiratory tissues were observed in rats, guinea pigs, rabbits, or dogs inhaling up to 6,700 ppm 1,3-butadiene for 7.5 hours/day, 6 days/week, for 8 months (Carpenter et al. 1944) or in rats or mice exposed to 8,000 ppm 1,3-butadiene for 6 hours/day, 5 days/week, for 13–14 weeks (Crouch et al. 1979; NTP 1984). No effects were observed in lungs of mice exposed to concentrations as high as 625 ppm for 6 hours/day, 5 days/week, for 9 months (NTP 1993).

An increase in chronic inflammation of the nasal cavity, fibrosis, cartilaginous metaplasia, osseous metaplasia, atrophy of the sensory epithelium, and hyperplasia of the respiratory epithelium were observed in mice exposed to 1,250 ppm for 2 years (NTP 1984). Lungs of rats exposed chronically to 8,000 ppm 1,3-butadiene exhibited metaplasia (Owen and Glaister 1990; Owen et al. 1987). Atrophy of the nasal olfactory epithelium was observed in mice exposed to concentrations as high as 1,250 ppm 1,3-butadiene for 6 hours/day, 5 days/week, for 61 weeks (NTP 1993), while alveolar epithelial hyperplasia (a possible precancerous lesion) occurred in mice exposed to 6.25 ppm 6 hours/day, 5 days/week for 2 years (NTP 1993).

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat	1 d 4 h/d				129000 (LC50)	Shugaev 1969	
2	Mouse	1 d 2h/d				122000 (LC50)	Shugaev 1969	
3	Rabbit	1 d 23 min/d				250000	Carpenter et al. 1944	
Systemic								
4	Rat	10 d 6 hr/d Gd 6-15	Bd Wt		200 F (decreased maternal body weight gain)	8000 F (45% decreased maternal body weight gain)	Irvine 1981	
Neurological								
5	Human	1 d 6-8 hr/d		8000			Carpenter et al. 1944	
6	Rabbit	1 d 23 min/d				250000 (anesthesia)	Carpenter et al. 1944	
Reproductive								
7	Mouse (B6C3F1)	5 d 6 h/d			1000 M (73% increase in number of abnormal sperm heads)		DOE/NTP 1988a	
8	Mouse CD-1	6 hr/day 5 days			200 M (increased intrauterine death)		DOE/NTP 1988b	

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Developmental								
9	Rat (Sprague-Dawley)	10 d 6 hr/d Gd 6-15		1000			DOE/NTP 1987a	
10	Rat	10 d 6 hr/d Gd 6-15		200	8000 (decreased fetal growth) 1000 (major skeletal malformations)		Irvine 1981	
11	Mouse (CD-1)	10 d 6 hr/d GD 6-15			40 M (decreased fetal BW in males)		DOE/NTP 1987b	
INTERMEDIATE EXPOSURE								
Death								
12	Mouse	14 wk 5 d/wk 6 hr/d				5000 (increased mortality)	NTP 1984	
13	Mouse (B6C3F1)	13-52 wk 6 hr/d 5 d/wk				200 (increased mortality from 40 weeks of exposure)	NTP 1993	

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Systemic								
14	Rat	13 wk 5 d/wk 6 hr/d	Resp	8000			Crouch et al. 1979	
			Cardio	8000				
			Hemato	8000				
			Musc/skel	8000				
			Hepatic	8000				
			Renal	8000				
			Dermal	8000				
			Ocular	8000				
15	Mouse	3-24 wk 6 d/wk 6 hr/d	Hemato			1250 M (macrocytic megaloblastic anemia starting at 6 weeks)	Irons et al. 1986a, b	

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
16	Mouse	14 wk 5 d/wk 6 hr/d	Resp	8000			NTP 1984	
			Cardio	8000				
			Gastro	8000				
			Musc/skel	8000				
			Hepatic	8000				
			Renal	8000				
			Dermal	8000				
			Bd Wt	1250	2500 M (13% decreased body weight)			
17	Mouse (B6C3F1)	13-52 wk 6 hr/d 5 d/wk	Resp		200 M (alveolar epithelial hyperplasia after 40 weeks)		NTP 1993	
			Cardio		200 M (endothelial hyperplasia after 40 weeks)			
			Ocular	200 M	625 M (Harderian gland hyperplasia after 26 weeks)			

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
18	Mouse (B6C3F1)	40 wk 6 hr/d 5 d/wk	Resp	200 M	625 M (alveolar epithelial hyperlasia)		NTP 1993	
			Cardio	625				
			Gastro	200	625 (forestomach epithelial hyperplasia)			
			Hemato		62.5 M (decreased erythrocyte counts, hemoglobin concentration, and red cell volume)	200 F (macrocytic megaloblastic anemia)		
			Musc/skel	625				
			Hepatic	625 F				
			Bd Wt	625				
Immuno/ Lymphoret								
19	Mouse (B6C3F1)	40 wk 6 hr/d 5 d/wk			625 F (19% reduction in relative thymus weight)		NTP 1993	
20	Mouse	6-24 wk 5 d/wk 6 hr/d			1250 (lymphoid organ histopathology)		Thurmond et al. 1986	
Neurological								
21	Rat	13 wk 5 d/wk 6 hr/d		8000			Crouch et al. 1979	

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
22	Mouse	14 wk 5 d/wk 6 hr/d		8000			NTP 1984	
Reproductive								
23	Mouse (CD)	10 wk 6 h/d 5 d/wk				12.5 M (increase in late fetal deaths, exencephalies, and skull abnormalities)	Anderson et al. 1996	
24	Mouse (CD)	4 wk 6 h/d 5 d/wk		12.5 M	65 M (increases in early fetal deaths)		Anderson et al. 1998	
25	Mouse (B6C3F1)	40 wk 6 hr/d 5 d/wk		62.5 F		200 F (ovarian atrophy)	NTP 1993	
Cancer								
26	Mouse (B6C3F1)	13-52 wk 6 hr/d 5 d/wk				200 M (CEL:lymphocytic lymphoma, histiocytic sarcoma, cardiac hemangiosarcoma, alveolar/bronchiolar adenoma/carcinoma, forestomach squamous cell papilloma/carcinoma, hepatocellular adenoma, Harderian gland adenoma/adenocarcinom preputial gland carcinoma)	NTP 1993	

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
CHRONIC EXPOSURE										
Death										
27	Rat	105-111 wk 5 d/wk 6 hr/d		1000			8000	(increased mortality)	Owen et al. 1987, Owen and Glaister 1990	
28	Mouse	61 wk 5 d/wk 6 hr/d					625	(increased mortality)	NTP 1984	
29	Mouse (B6C3F1)	2 yr 6 hr/d 5 d/wk					20	(increased mortality)	NTP 1993	
Systemic										
30	Rat	105-111 wk 5 d/wk 6 hr/d	Resp	1000	8000	(increased organ weight, metaplasia)			Owen et al. 1987, Owen and Glaister 1990	
			Cardio	8000						
			Gastro	8000						
			Hemato	8000						
			Hepatic	8000						
			Renal	1000			8000	(nephrosis)		
			Dermal	8000						
			Ocular	8000						

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
31	Mouse	61 wk 5 d/wk 6 hr/d	Resp	625		1250 (atrophy of nasal olfactory epithelium)	NTP 1984	
			Cardio		625 (endothelial hyperplasia)			
			Gastro		625 (epithelial hyperplasia)			
			Musc/skel	1250				
			Hepatic		625 (hepatic necrosis)			
			Renal	1250				
			Dermal	1250				
32	Mouse (B6C3F1)	2 yr 6 hr/d 5 d/wk	Resp		6.25 M (alveolar epithelial hyperplasia)		NTP 1993	
			Cardio	200	625 (endothelial hyperplasia)			
			Gastro		625 F (forestomach epithelial hyperplasia)			
					200 F (forestomach epithelial hyperplasia)			
			Musc/skel	625				
			Hepatic		62.5 (liver necrosis)			
			Bd Wt	625				

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
33	Mouse (B6C3F1)	65 wk 6 hr/d 5 d/wk	Hemato	200		625	(macrocytic megaloblastic anemia)	NTP 1993	
			Bd Wt	625					
Neurological									
34	Rat	105-111 wk 5 d/wk 6 hr/d		8000				Owen et al. 1987, Owen and Glaister 1990	
35	Mouse	61 wk 5 d/wk 6 hr/d		1250				NTP 1984	
Reproductive									
36	Rat	105-111 wk 5 d/wk 6 hr/d		8000				Owen et al. 1987, Owen and Glaister 1990	Only examined histopathology
37	Mouse	61 wk 5 d/wk 6 hr/d				625	(gonadal atrophy)	NTP 1984	
38	Mouse (B6C3F1)	2 yr 6 hr/d 5 d/wk				6.25 F	(ovarian atrophy)	NTP 1993	
39	Mouse (B6C3F1)	65 wk 6 hr/d 5 d/wk		20 F		62.5 F	(ovarian atrophy)	NTP 1993	

Table 3-1 Levels of Significant Exposure to 1,3-butadiene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Cancer								
40	Rat	105-111 wk 5 d/wk 6 hr/d				1000 (CEL: mammary gland adenoma and sarcoma)	Owen et al. 1987, Owen and Glaister 1990	
41	Mouse	61 wk 5 d/wk 6 hr/d				625 (CEL:alveolar/bronchiolar adenoma or carcinoma, malignant lymphoma, hemangiosarcoma, forestomach squamous cell papilloma or carcinoma, mammary gland carcinoma, ovarian granulosa cell tumor)	NTP 1984	
42	Mouse (B6C3F1)	2 yr 6 hr/d 5 d/wk				6.25 F (CEL: alveolar/bronchiolar adenoma/carcinoma)	NTP 1993	

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

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = Female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to 1,3-Butadiene - Inhalation

Acute (≤14 days)

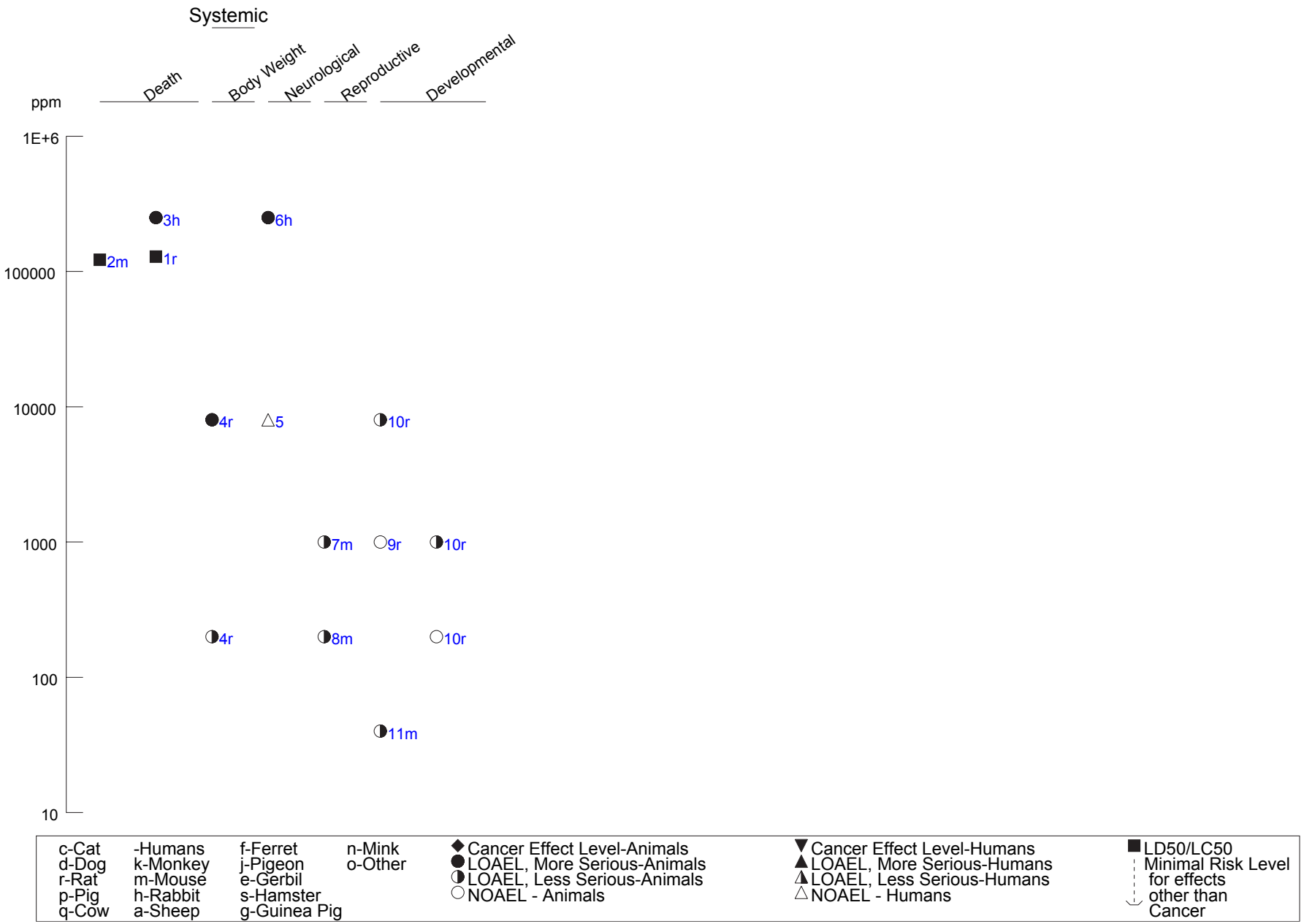


Figure 3-1 Levels of Significant Exposure to 1,3-Butadiene - Inhalation *(Continued)*

Intermediate (15-364 days)

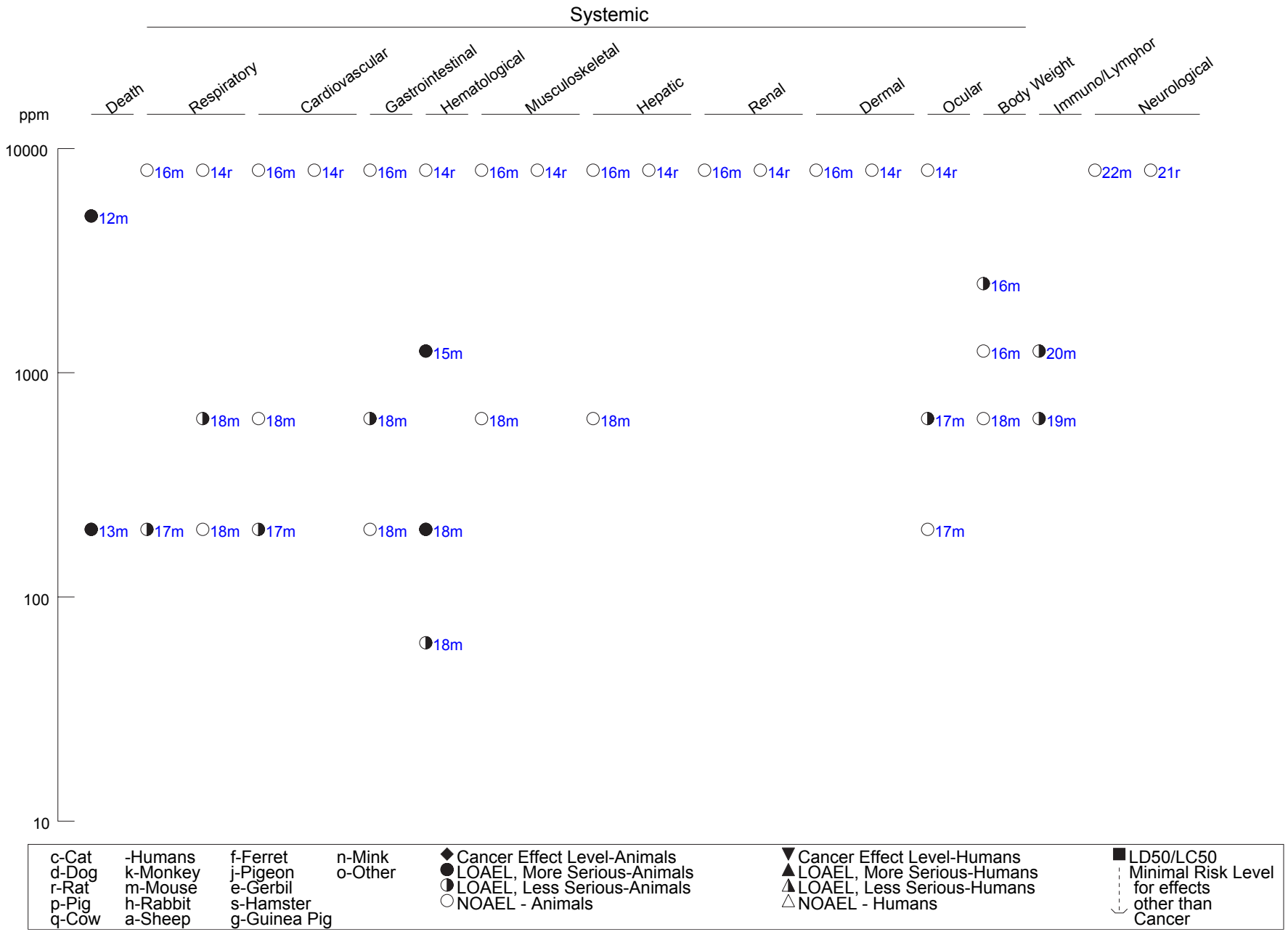


Figure 3-1 Levels of Significant Exposure to 1,3-Butadiene - Inhalation *(Continued)*

Intermediate (15-364 days)

Figure 3-1 Levels of Significant Exposure to 1,3-Butadiene - Inhalation *(Continued)*

Chronic (≥365 days)

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

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

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

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

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

Cardiovascular Effects. In a retrospective epidemiological study of middle-aged workers in the rubber industry, excessive mortality was noted for certain types of cardiovascular diseases, mainly chronic rheumatic and arteriosclerotic heart diseases (McMichael et al. 1974). Furthermore, increased mortality for arteriosclerotic heart disease was reported among black males in the rubber industry (Matanoski and Schwartz 1987). This result was also reported in an update of the original study (Matanoski et al. 1988, 1990). However, increased mortality from cardiovascular disease was not observed in three other cohorts of SBR and 1,3-butadiene monomer workers (Cowles et al. 1994; Divine and Hartman 1996, 2001; Ward et al. 1995). Thus, it is unclear if cardiovascular disease is likely to be caused by 1,3-butadiene exposure.

No cardiovascular lesions were found in mice or rats exposed to 8,000 ppm 1,3-butadiene 6 hours/day, 5 days/week, for 13–14 weeks (Crouch et al. 1979; NTP 1984). Endothelial hyperplasia in the heart (an early preneoplastic lesion) was observed in mice after exposure to 200 ppm for 6 hours/day, 5 days/week for 40 weeks (NTP 1993) or 625 ppm 6 hours/day, 5 days/week for 61 weeks or 2 years (NTP 1984, 1993). No exposure-related histopathological cardiac lesions were found in rats exposed chronically to up to 8,000 ppm for 2 years (Owen et al. 1987).

Gastrointestinal Effects. No studies were located regarding noncancer gastrointestinal effects in humans after inhalation exposure to 1,3-butadiene.

No significant incidences of gastrointestinal tract lesions were observed in mice following exposure to 8,000 ppm 1,3-butadiene for 6 hours/day, 5 days/week, for 14 weeks (NTP 1984) or 200 ppm for 6 hours/day, 5 days/week for 40 weeks (NTP 1993). In a chronic-duration study, high incidences of forestomach epithelial hyperplasia (a possible preneoplastic lesion) were observed in mice exposed to 625 ppm for 6 hours/day, 5 days/week for 61 weeks (Melnick et al. 1990a; NTP 1984) and for 2 years (NTP 1993). No exposure-related nonneoplastic gastrointestinal lesions were found in rats exposed chronically to up to 8,000 ppm for 6 hours/day, 5 days/week for 2 years (Owen et al. 1987).

Hematological Effects. A hematological survey of workers at a styrene-butadiene rubber plant revealed little indication of bone marrow toxicity among the workers (Checkoway and Williams 1982). Styrene and 1,3-butadiene were the most significant chemicals in the atmosphere; benzene and toluene were present in much lower concentrations. A group of eight tank farm workers (workers who load and unload chemicals from storage tanks; mean level exposure of 20 ppm) demonstrated slightly lower levels

of red blood cells, hemoglobin, platelets, and neutrophils compared with other workers, but these findings were within the normal range. Tsai et al. (2005) examined a number of hematological end points in a petrochemical production facility in which the current time-weighted average (TWA) 1,3-butadiene exposure level was 0.25 ppm; prior to 1997, the TWA concentration was 4.55 ppm. As compared to unexposed controls, no significant alterations in total or differential leukocyte levels, erythrocyte levels, hemoglobin levels, mean corpuscular volume, or platelet levels were found. An older study of workers from one of the facilities examined by Tsai et al. (2005) also found no significant alterations in total and differential leukocyte levels, erythrocyte levels, hemoglobin levels, platelet levels, or mean corpuscular volume (Cowles et al. 1994); the mean 1,3-butadiene concentration was 3.5 ppm.

No signs of blood dyscrasias were found among 164 animals (rats, rabbits, guinea pigs, dogs) exposed to concentrations up to 6,700 ppm of 1,3-butadiene for 8 months (Carpenter et al. 1944). The results were supported by a 3-month study in which no effects on hematological indices were found in rats after exposure to 8,000 ppm of 1,3-butadiene (Crouch et al. 1979).

A treatment-related macrocytic megaloblastic anemia was observed in B6C3F1 and NIH mice exposed to 1,250 ppm 1,3-butadiene for 6 hours/day, 6 days/week for 6–24 weeks, but not after a 3-week exposure to the same concentration (Irons et al. 1986a, 1986b). The bone marrow damage was expressed as reduced numbers of red blood cells, decreased hemoglobin concentration and hematocrit, and increased mean corpuscular volume of circulating erythrocytes. The changes were observed in both strains, independently of the occurrence of murine leukemia viruses in the animals. Male mice exposed to ≥62.5 ppm for 6 hours/day, 5 days/week for 40 weeks exhibited decreased red blood cell counts, hemoglobin concentration, and hematocrit (NTP 1993). Leukopenia and lymphopenia occurred at ≥200 ppm. Females exhibited macrocytic megaloblastic anemia and bone marrow atrophy after exposure to 200 and 625 ppm, respectively, 6 hours/day, 5 days/week for 40 weeks (NTP 1993).

Macrocytic megaloblastic anemia and bone marrow hyperplasia was also observed in mice exposed chronically to 625 ppm 1,3-butadiene 6 hours/day, 5 days/week for 65 weeks (NTP 1993). Surviving females, but not males, in this study exhibited increased bone marrow cellularity.

In contrast to the findings in mice, no effects on hematology or blood chemistry of Sprague-Dawley rats were observed after exposure to 1,000 and 8,000 ppm of 1,3-butadiene for 105–111 weeks (Owen et al. 1987).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects of 1,3-butadiene in humans after inhalation exposure.

No musculoskeletal effects were observed in mice and rats exposed to 8,000 ppm 1,3-butadiene 6 hours/day, 5 days/week for 13–14 weeks (Crouch et al. 1979; NTP 1984) or in mice exposed to 625 ppm 6 hours/day, 5 days/week from 40 or 65 weeks or 2 years (NTP 1993).

Hepatic Effects. No studies were located regarding hepatic effects of 1,3-butadiene in humans after inhalation exposure.

No histopathological changes in livers of rats (Crouch et al. 1979) or mice (NTP 1984) were found after intermediate-duration exposure to 1,3-butadiene. The relative liver weights of both sexes of Sprague-Dawley rats were elevated after the chronic exposure to 1,3-butadiene (1,000 and 8,000 ppm); however, this finding was not associated with any pathological changes (Owen et al. 1987). Mice exposed to ≥625 ppm 6 hours/day, 5 days/week for 61 weeks had a significant increase in liver necrosis (NTP 1984).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,3-butadiene.

The results of urinalysis in 164 animals, including rats, guinea pigs, rabbits, and dogs were all normal after an 8-month exposure to concentrations up to 6,700 ppm of 1,3-butadiene (Carpenter et al. 1944), but the methods were poorly described. These results were supported, however, in rats after 13 weeks of exposure to concentrations up to 8,000 ppm of 1,3-butadiene (Crouch et al. 1979). Nephrosis was found among male rats after 111 weeks of exposure to 8,000 ppm, but not 1,000 ppm, of 1,3-butadiene (Owen et al. 1987). No non-neoplastic renal lesions were observed in mice exposed to 8,000 ppm 6 hours/day, 5 days/week for 14 weeks (NTP 1984) or 625 ppm 6 hrs/day, 5 days/week, for 40 weeks to 2 years.

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to 1,3-butadiene.

No histopathological dermal changes were found in rats or mice after 13–14 weeks exposure to 8,000 ppm 1,3-butadiene (Crouch et al. 1979; NTP 1984), in rats after 111 weeks exposure to 8,000 ppm (Owen et al. 1987), or in mice after 40 weeks to 2 years exposure to 625 ppm (NTP 1993).

Ocular Effects. Two men reported slight irritation of the eyes and difficulty in focusing on instrument scales during 6–7 hours exposure to 2,000 and 4,000 ppm 1,3-butadiene (Carpenter et al. 1944).

Ophthalmologic examination of the eyes of dogs and rabbits disclosed no signs of injury during the course of exposure to up to 6,700 ppm 1,3-butadiene for 8 months (Carpenter et al. 1944). After the termination of the experiment, histological examination revealed that the sclera, cornea, and ciliary body were normal. Sections of the optic nerve with adjacent retina showed no myelin sheath degeneration. Although the ophthalmological examination was described in detail, the study was limited by the small number of animals used.

No histopathological ocular changes were found in rats or mice after 13–14 weeks exposure to 8,000 ppm (Crouch et al. 1979; NTP 1984) or in rats after 111 weeks exposure to 8,000 ppm 1,3-butadiene (Owen et al. 1987). Increased Harderian gland hyperplasia (a precancerous lesion) was observed in male mice exposed to ≥62.5 ppm 6 hours/day, 5 days/week for 65 weeks and 2 years (NTP 1993); this effect is not relevant to humans because they do not have Harderian glands.

Body Weight Effects. Body weights were reduced by 13% in male mice exposed to 2,500 ppm 1,3-butadiene 6 hours/day, 5 days/week for 14 weeks, but were not significantly different from controls when exposed to 1,250 ppm 6 hours/day, 5 days/week for 61 weeks or when exposed to 625 ppm 6 hours/day, 5 days/week for 2 years (NTP 1993)

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects of 1,3-butadiene in humans after inhalation exposure.

After 3–21 weeks of exposure to 1,250 ppm 1,3-butadiene, an increased expression of murine leukemia virus (MuLV) was observed in hematopoietic tissues of B6C3F1 mice, but not in NIH mice (Irons et al. 1987a). Furthermore, altered regulation of the stem cell development in B6C3F1 mice was reported after a similar exposure (Leiderman et al. 1986).

Intermediate-duration exposure of female mice to 62.5 ppm 1,3-butadiene 6 hours/day, 5 days/week for 40 weeks resulted in a 17% reduction in relative spleen weight, while exposure to 625 ppm for the same

duration resulted in a 19% reduction in thymus weight (NTP 1993). By 65 weeks, relative spleen weights in 625 ppm females had increased to 57% higher than controls.

Immunological changes were detected after evaluation of specific humoral and cell-mediated immunity in B6C3F1 mice exposed to 1,250 ppm 1,3-butadiene for 6, 12, or 24 weeks (Thurmond et al. 1986). Suppression of cytotoxic T-lymphocyte generation to mastocytoma cells was observed after 6 weeks, but recovered after 12 weeks of exposure. The histological examination of lymphoid organs showed depressed spleen cellularity after 24 weeks of exposure; this value is recorded as a LOAEL for immunological effects in Table 3-1 and plotted in Figure 3-1, although it is not known how these changes affect immunocompetency.

3.2.1.4 Neurological Effects

Psychomotor responses of two men inhaling 2,000, 4,000, or 8,000 ppm 1,3-butadiene for 6–8 hours/day on different days were evaluated by Carpenter et al. (1944). At the two higher concentrations, the subjects performed a steadiness test; at the highest concentration, a tapping rate test was also performed. Results after 1,3-butadiene exposure were identical to those obtained before exposure.

Rabbits exposed to 250,000 ppm of 1,3-butadiene went through all stages of anesthesia to death in the average time of 23 minutes (Carpenter et al. 1944). Less than 2 minutes of exposure was required for loss of motor and labyrinth reflexes.

No effects on erythrocyte or brain cholinesterase or on neuromuscular function tests were found in rats exposed to up to 8,000 ppm for 13 weeks (Crouch et al. 1979). In intermediate and chronic exposure studies in mice and rats, no treatment-related histopathological lesions were found in organs and tissues of the nervous system (brain, spinal cord, sciatic nerves) (Crouch et al. 1979; NTP 1984; Owen and Glaister 1990; Owen et al. 1987). Tests results for neurological function (i.e., loss of balance on a rotating cone) were possibly confounded by the mammary tumors interfering with the mobility of rats (NTP, 1984). The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 1,3-butadiene. A concentration-related increase in the incidence of sperm-head abnormalities occurred in

B6C3F1 mice after exposure to 1,000 (73% increase) and 5,000 ppm (129% increase) of 1,3-butadiene 6 hours/day for 5 days (DOE/NTP 1988a). No impairment of fertility was noted when groups of male and female rats, rabbits, or guinea pigs were exposed to ≤6,700 ppm 1,3-butadiene (Carpenter et al. 1944).

No treatment-related histopathological effects were seen in reproductive organs of rats or mice exposed to 8,000 ppm 1,3-butadiene 6 hours/day, 5 days/week for 13–14 weeks (Crouch et al. 1979; NTP 1984). Reduction in the number of round and elongated sperm heads was seen in mice exposed to 130 ppm 6 hours/day, 5 days/week for 4 weeks, but this was not associated with changes in fertility (Anderson et al. 1998). Ovarian and uterine atrophy occurred in female mice exposed to 200 ppm 6 hours/day, 5 days/week for 40 weeks (NTP 1993), while testicular atrophy was seen in male mice exposed to 625 ppm for the same duration. Exposure of female mice to 62.5 or ≥6.25 ppm 1,3-butadiene 6 hours/day, 5 days/week for 65 weeks or 2 years, respectively, resulted in an increased incidence of ovarian atrophy (NTP 1993). Affected females had no evidence of oocytes, follicles, or corpora lutea. An increase in testicular atrophy and preputial gland hyperplasia was observed in males only after exposure to 625 ppm 6 hours/day, 5 days/week for 2 years (NTP 1993). In contrast, no histological alterations were observed in the gonads of rats exposed to up to 8,000 ppm 6 hours/day, 5 days/week for 2 years (Owen et al. 1987).

In untreated female mice mated with males exposed to ≥200 ppm 6 hours/day for 5 days, a significant increase in the number of females with two or more intrauterine deaths were observed (DOE/NTP 1988b). This effect was only observed in animals mated during the first week post-exposure. Additional effects included increases in early implantation loss at 1,000 ppm during the first post-week of exposure and at 200 and 1,000 ppm during the second week post-exposure; implantation losses were not significantly increased in the mice exposed to 5,000 ppm. Early fetal death was also observed in untreated female mice mated to males exposed to 65 ppm for 6 hours/day, 5 days/week for 4 weeks (DOE/NTP 1988a). Fetal toxicity was observed following the mating of untreated female mice with males exposed to 12.5 ppm 1,3-butadiene 6 hours/day, 5 days/week for 10 weeks (Anderson et al. 1996). Observed effects included an increase in late fetal death, exencephaly, and skull abnormalities.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,3-butadiene.

When exposed to concentrations up to 8,000 ppm 1,3-butadiene for 6 hours/day, 5 days/week during GDs 6–15, Sprague-Dawley rats showed signs of dose-related maternal and fetal toxicity (Irvine 1981). Depressed body weight gain among dams was observed at ≥200 ppm, and fetal growth (body weight and crown-rump length) was significantly decreased in the 8,000 ppm group. A significant increase in the number of litters with fetuses showing minor skeletal defects was observed at 200 ppm, but not at 1,000 or 8,000 ppm; however, an increase in the number of fetuses with irregular ossification was observed at 8,000 ppm. Significant increases in the number of litters with fetuses showing major skeletal defects were observed at 1,000 and 8,000 ppm. The majority of the major skeletal defects were wavy ribs; abnormalities of the skull, spine, sternum, long bones, and ribs were also observed at 8,000 ppm. A significant increase in the number of litters with fetuses showing minor external/visceral defects was observed at 1,000 ppm, but not at 8,000 ppm. In a study in which female Sprague-Dawley rats were exposed to 40–1,000 ppm during GDs 6–15 (DOE/NTP 1987a), some skeletal abnormalities and ossification reductions were found in the fetuses, but were not statistically significant and were not considered to be treatment-related. In mice, a 5–23% decrease in fetal body weight gain, primarily among male mice, was observed after exposure of dams during GDs 6–15 to 40–1,000 ppm 1,3-butadiene. The magnitude of the decreased fetal body weight in males was 5, 18, and 23% in the 40, 200, and 1,000 ppm groups, respectively. The investigators reported that the decreased fetal body weight was statistically significant in males at all dose levels; however, the statistical method used (ANOVA) did not account for differences in litter size. Increased incidences of extra ribs and reduced ossification of sternebrae were found in fetuses from groups exposed to 200 ppm and 1,000 ppm, respectively (DOE/NTP 1987b).

The highest NOAEL value and all reliable LOAEL values for developmental effects in rats for the acute duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

Retrospective epidemiological studies of mortality among workers in the rubber industry were conducted in SBR (polymer) production workers and 1,3-butadiene monomer workers. For SBR workers, the primary cohort is comprised of largely overlapping cohorts from multiple SBR facilities in the United

States and Canada examined by investigators at John Hopkins (Matanoski and Schwartz 1987; Matanoski et al. 1989b, 1990) and the University of Alabama at Birmingham (Cheng et al. 2007; Delzell et al. 1996; Graff et al. 2005; Macaluso et al. 1996; Sathiakumar et al. 2005, 2007). Mortality among three independent cohorts of male 1,3-butadiene monomer production workers has been studied and updated on several occasions, including cohorts from Union Carbide (Ward et al. 1995), Texaco (Divine 1990; Divine et al. 1993), and Shell (Cowles et al. 1994).

Matanoski et al. 1990 (in an update of the Matanoski and Schwartz 1987 cohort) found increased standardized mortality ratios (SMRs) of 532 (1 case), 656 (95% confidence interval [CI]=135–1,906), and 482 (95% CI=59–1,762) for lymphosarcoma, leukemia, and other lymphatic neoplasms, respectively, in black SBR production workers; white workers exhibited an SMR of 230 (95% CI=92–473) for other lymphatic neoplasms. In white maintenance workers, SMRs of 144 (95% CI=53–314) and 166 (95% CI=93–275) were observed for esophageal and stomach cancer, respectively. An odds ratio of 9.4 for leukemia was observed in SBR workers in a nested case-control study of the Matanoski and Schwartz (1987) cohort of SBR workers (Matanoski et al. 1989b). No such association was found for exposure to styrene. Several investigators at the University of Alabama at Birmingham examined cancer mortality in a cohort of over 15,000 North American SBR workers (Cheng et al. 2007; Delzell et al. 1996; Graff et al. 2005; HEI 2006; Macaluso et al. 1996; Sathiakumar et al. 2005, 2007). Delzell et al. (1996) found increased SMRs for leukemia of 265 (95% CI=141–453) for maintenance and 431 (95% CI=207–793) for laboratory workers. Macaluso et al. (1996) derived a relative rate value of 4.5 for leukemia development (no confidence interval reported) associated with a cumulative exposure of 80 ppm-years. In an update of these studies (Sathiakumar et al. 2005), an increase in deaths from all types of leukemia (SMR of 258; 95% CI=156–403) was found among hourly employees with 20–29 years since hire and >10 years of employment. Increases in leukemia deaths were also found among workers in the polymerization (SMR of 204; 95% CI=121–322), maintenance labor (SMR of 326; 95% CI=178–456), and laboratory (SMR of 326; 95% CI=178–546) operations. However, no increases in a specific type of leukemia were found. Similarly, Graff et al. (2005) reported increased relative risks for leukemia of 2.9 (95% CI=1.4–6.4) and 3.7 (95% CI=1.7–8.0) among workers with cumulative 1,3-butadiene exposures of 184.7–<435.0 and 425.0 ppm-years. When the relative risks were adjusted for exposure to styrene and dimethyldithio-carbamate, age, and years since hire, only the highest cumulative exposure group had a confidence interval that included 1 (relative risk of 3.0, 95% CI=1.0–9.2). When workers were divided into two categories based on exposure to >100 and ≤100 ppm, associations between 1,3-butadiene cumulative exposure and leukemia were found for both groups, although the association was weaker at the lower concentration (relative risk of 2.0; 95% CI=0.6–6.0 for cumulative exposure to >124.7 ppm-years) than at

the higher concentration (relative risk of 3.7; 95% CI=1.3–11.1 for cumulative exposure of >247.6 ppm-years) and the trend was only statistically significant in the >100 ppm workers (HEI 2006). A more recent paper by Graff and associates (Graff et al. 2009) used uncertainty analysis to evaluate the impact of potential exposure estimate inaccuracies on the leukemia relative risks. The investigators concluded that analysis of the complete probability distribution of 1,3-butadiene exposure estimate supported the association between 1,3-butadiene cumulative exposure and increased leukemia risk. Using personal monitoring device data collected from 1977 to 1991, Sathiakumar et al. (2007) compared measured 1,3-butadiene levels with estimated levels. The mean measured 1,3-butadiene level (across all years and job categories) was 5.2 ppm and the mean estimated concentration was 4.7 ppm; the estimated 1,3-butadiene levels tended to underestimate concentrations that were greater than 7 ppm. Cheng et al. (2007) found a significant trend for the association of leukemia in SBR workers and increasing cumulative exposure or number of "peak" exposures (>100 ppm). They also reported a minimal association (relative rate of 1.03) of leukemia in SBR workers receiving an estimated 5 ppm 1,3-butadiene exposure for 20 years (100 ppm-years). Examination of possible associations between 1,3-butadiene exposure and increased deaths from other cancer types, including non-Hodgkin's lymphoma, Hodgkin's lymphoma, and multiple myeloma were not found in this cohort (HEI 2006). Increases in the risk of colorectal and prostate cancer were observed in some subgroups of SBR workers; however, no consistent exposure-response trends were found (HEI 2006).

These results in SBR workers with 1,3-butadiene exposure are supported by studies in 1,3-butadiene monomer production workers. Downs et al. (1987) calculated an SMR of 235 (no CI reported) for lymphosarcoma and reticular cell sarcoma. No increase in mortality from cancer of gastrointestinal, respiratory, urinary, and skeletal systems was associated with monomer exposure. Divine (1990) and Divine et al. (1993) reported similar results in a follow-up study of this cohort (SMR of 452 [95% CI=165–984]) for lymphosarcoma. Divine and Hartman (2001) followed this cohort for an additional 5 years and found a statistically significant increase in SMR (141; 95% CI=105–186) for all lymphohematopoietic cancer. Subcohort analyses showed that increases in lymphohematopoietic cancers appear to be restricted to monomer workers employed before 1950 and for the shortest duration (Divine and Hartman 1996, 2001). Elevations were also seen for leukemia (SMR of 129; 95% CI=77–204) and non-Hodgkin's lymphoma (SMR of 148; 95% CI=89–231), but the elevation was not statistically significant. Additionally, higher SMRs for leukemia and non-Hodgkin's lymphoma were found in workers with shorter employment durations. No significant associations were found between cumulative 1,3-butadiene exposure (defined as a combination of job exposure class, calendar time, and length of time in job) and the relative risk for lymphohematopoietic cancers, leukemia, or non-Hodgkin's lymphoma

(Divine and Hartman 2001). Analysis of another cohort of 364 monomer workers, 277 of which worked in a U.S. Rubber Reserve plant during World War II, found an SMR of 577 (95% CI=157–1,480) for lymphosarcoma and reticulosarcoma (Ward et al. 1995). No significant association was found between 1,3-butadiene monomer exposure and all, lung, or lympho-hematopoietic cancers in a cohort of 614 monomer workers employed between 1948 and 1989 who were exposed to a relatively low mean concentration of 3.5 ppm, with many measurements below 1 ppm (Cowles et al. 1994).

The major limitations of the epidemiological studies described so far include the lack of precise historic exposure data to 1,3-butadiene, lack of adjustment for smoking, and possible exposure to other chemicals. Irons and Pyatt (1998) suggest that dithiocarbamates, such as dimethyldithiocarbamate (DMDTC), used in the SBR vulcanization process from 1950 to 1965, may have played a significant role in leukemia development that was concentrated in workers employed during this period. However, Santos-Burgoa et al. (1992) and Delzell et al. (2001) and HEI (2006) used multivariate analysis to suggest that the estimates of 1,3-butadiene exposure provided the best correlation with the rates of leukemia, even in the presence of styrene and DMDTC.

Several investigators have evaluated associations between childhood leukemias and ambient 1,3-butadiene emissions. Knox et al. (2005, 2006) associated the occurrence of childhood cancer with proximity of birthplace to industrial 1,3-butadiene and benzene emissions, and roads, railways, waterways, and bus, ferry, or train stations in Great Britain; however, no actual exposure data or estimates were available. Reynolds et al. (2003) calculated leukemia rate ratios (RR), adjusted for age, ethnicity, and sex, of 1.21 (95% CI=1.03–1.42) and 1.32 (95% CI=1.11–1.57) for children in California census tracts ranked highest for combined exposure to 25 hazardous air pollutants (HAPs, including 1,3-butadiene) and highest for point-source HAP exposures, respectively. Likewise, Whitworth et al. (2008) reported a significant association of childhood leukemia incidence with residence in census tracts close to the ship channel (which is in close proximity to petrochemical and chemical manufacturing facilities) in Houston, Texas. These studies do not indicate strong causality between 1,3-butadiene exposure and childhood leukemia, as many chemicals may have contributed to exposure and the actual exposure to 1,3-butadiene, if any, is unknown.

The rodent bioassay database corroborates the association of lympho-hematopoietic neoplasms and occupational exposure to 1,3-butadiene reported in the epidemiology literature. Mice were clearly more sensitive to 1,3-butadiene-mediated tumor development than rats. In rats, increased tumors were not observed following intermediate-duration exposures of up to 8,000 ppm 1,3-butadiene 6 hours/day,

5 days/week for 13 weeks (Crouch et al. 1979). Two-year exposure of rats to 1,000 or 8,000 ppm 6 hours/day, 5 days/week resulted in increased incidences of Leydig cell adenoma, pancreatic exocrine adenoma, uterine sarcoma, mammary gland adenoma and carcinoma, Zymbal gland carcinoma, and thyroid follicular cell tumors (Owen and Glaister 1990; Owen et al. 1987). In mice, exposure to 200 ppm for 40 weeks resulted in increased incidences of lymphocytic lymphoma, histiocytic sarcoma, cardiac hemagiosarcoma, alveolar/bronchiolar adenoma/carcinoma, forestomach squamous cell papilloma/carcinoma, hepatocellular adenoma, hardarian gland adenoma/adenocarcinoma, and preputial gland carcinoma (NTP 1993). These same tumors developed in mice in as little as 13 weeks after exposure to 625 ppm 6 hours/day, 5 days/week (NTP 1993). Chronic exposure of mice to lower concentrations of 1,3-butadiene also resulted in multi-target organ neoplasm development. Two-year 6-hour/day, 5-day/week exposures of 20 ppm for male mice and 6.25 ppm (the lowest exposure level tested) for female mice resulted in increased incidences of lymphocytic lymphoma, histiocytic sarcoma, cardiac hemagiosarcoma, alveolar/bronchiolar adenoma/carcinoma, forestomach squamous cell papilloma/carcinoma, hepatocellular adenoma, hardarian gland adenoma/adenocarcinoma, mammary gland carcinoma, adenocanthoma, malignant mixed tumor, and malignant ovarian granulosa cell tumor.

The cancer effect levels (CELs) are recorded in Table 3-1 and plotted in Figure 3-1.

Using the Poisson regression analysis by Health Canada (2000) of the leukemia risk data from a cohort of 15,000 SBR production workers (Delzell et al. 1996), EPA derived a unit risk for inhalation exposure of 0.08 ppm^{-1} (IRIS 2012). This unit risk corresponds to upper bound individual lifetime cancer risks at 10^{-4}–10^{-6} for exposure levels of $1x10^{-3}$–$1x10^{-6}$ ppm, which are plotted in Figure 3-1. It should be noted that EPA derived the cancer risk levels in 2001, and thus, these values may not reflect the results of more recent studies of SBR workers.

The International Agency for Research on Cancer (IARC) has classified 1,3-butadiene as a Group 1 carcinogen (carcinogenic to humans) (IARC 2009). EPA has classified 1,3-butadiene as carcinogenic to humans (EPA 2002; IRIS 2012). The Department of Health and Human Services (NTP 2005) also identified 1,3-butadiene as a “known human carcinogen”.

3.2.2 Oral Exposure

No studies were located regarding health effects in humans or animals after oral exposure to 1,3-butadiene.

3.2.3 Dermal Exposure

Dermal contact with liquid 1,3-butadiene causes a sensation of cold followed by a sensation of burning, which is the result of rapid expansion of pressurized 1,3-butadiene from liquid to gas states (NIOSH, 2005). Although this may cause frostbite, it is specific to an unusual exposure scenario and is not a toxic endpoint. However, the possible toxic effects from dermal absorption of such a concentrated amount of 1,3-butadine are unknown. High gas concentrations may cause mild skin irritation as well (NIOSH, 2005). No other studies were located regarding health effects in humans or animals following dermal exposure to 1,3-butadiene.

3.3 GENOTOXICITY

1,3-Butadiene has been tested for genotoxicity in a number of *in vitro* and *in vivo* studies (Tables 3-2 and 3-3). Positive results have been found in the reverse mutation assay in *Salmonella typhimurium* TA1530 and TA1535 in the absence or in the presence of metabolic activation system (de Meester et al. 1978; Madhusree et al. 2002). However, the interpretation of these results was confounded by the fact that the Petri dishes not containing S-9 mix were contaminated by volatile active metabolites. It was concluded that S-9 mix was necessary to activate 1,3-butadiene into mutagen(s) (De Meester 1988). TA1530 was the most sensitive strain, but 1,3-butadiene mutagenicity was detectable only with metabolic activation in the subsequent study (de Meester et al. 1980). No significant mutagenic effect on *S. typhimurium* strain TA100 with metabolic activation was observed (Victorin and Stahlberg 1988). A weak genotoxic activity was detected in strain TA1535 with rat S-9 (Arce et al. 1989). A weak increase in sister chromatid exchanges was observed in Chinese hamster ovary cells, but only with metabolic activation (Sasiadek et al. 1991). Increased mutations occurred in the hypoxanthione-guanine phosphoribosyl transferase (*hprt)* and *tk* gene loci of human TK6 lymphoblastoid cells (Cochrane and Skopek 1993). On the basis of these data, 1,3-butadiene appears to require metabolic activation to produce genotoxicity.

The genotoxicity of 1,3-butadiene has been examined in several occupational exposure cohorts. Ward et al. (1994) reported a significant increase in hypoxanthine-guanine phosphoribosyltransferase (*hprt*) mutant frequency (measured in peripheral lymphocytes) among eight workers at a Texas 1,3-butadiene production plant working in the area of the plant where the highest 1,3-butadiene exposure occurred, as compared to levels in five workers in an area with low 1,3-butadiene exposures or in six controls who did not work at the 1,3-butadiene production plant. The mean area and personal 1,3-butadiene levels were 3.5 ppm (although most individual samples were <1 ppm) in the high-exposure area and 0.03 ppm in the

Table 3-2. Genotoxicity of 1,3-Butadiene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium				
TA1530	Gene mutation	+	–	de Meester et al. 1980
TA100	Gene mutation	–	–	Victorin and Stahlberg 1988
TA1535	Gene mutation	+	–	Arce et al. 1989; Madhusree et al. 2002
Eukaryotic organisms:				
Chinese hamster ovary	SCE	+	–	Sasiadek et al. 1991
Human TK6 lymphoblastoid cells	*hprt* and *tk* loci mutations	NA	NA	Cochrane and Skopek 1993

– = negative result; + = positive result; NA = not applicable; SCE = sister chromatid exchange

Table 3-3. Genotoxicity of 1,3 Butadiene *In Vivo*

Species (test system)	End point	Results	Reference
B6C3F1 mice (inhalation)	Bone marrow: Dose-dependent increase in SCEs	+	Cunningham et al. 1986
Sprague-Dawley rats (inhalation)		-	
B6C3F1 mice (inhalation)	Bone marrow: increase in CAs, SCEs, and AGT, and depression of MI	+	Tice et al. 1987
Swiss mice (inhalation)	Peripheral blood erythrocytes: induction of micronuclei	+	Irons et al. 1986b
B6C3F1 mice (inhalation)	Bone marrow: alteration of hematopoietic stem cell development	+	Leiderman et al. 1986
B6C3F1 mice (inhalation)	Peripheral blood erythrocytes: induction of micronuclei	+	Jauhar et al. 1988
B6C3F1 mice (inhalation)	Induction of MN; induction of SCEs; CAs	+	Tice et al. 1988
B6C3F1 mice (inhalation)	Sperm abnormalities; dominant lethality	+	DOE/NTP 1988a
C57B1/6 mice (intraperitoneal injection)	Bone marrow increase in CAs and SCEs	+	Sharief et al. 1986
B6C3F1 mice (inhalation)	*lacZ*$^-$ mutant frequency in lung	+	Recio et al. 1992
B6C3F1 mice (inhalation)	*lacZ*$^-$ mutant frequency in liver and bone marrow	-	Recio et al. 1992
B6C3F1 mice and F344 rats (inhalation)	*hprt* loci mutations in splenic T lymphocytes	+	Cochrane and Skopek 1993; Meng et al. 1999, 2000, 2004, 2007
B6C3F1 mice (inhalation)	Peripheral blood erythrocytes and bone marrow: induction of micronuclei	+	Autio et al. 1994
Wistar rats	Peripheral blood erythrocytes and bone marrow: induction of micronuclei	-	Autio et al. 1994
C3H mice (inhalation)	Heritable spermatid chromosomal translocations; dominant lethality	+	Adler et al. 1998
C3H mice (inhalation)	Spermatocytes: induction of micronuclei	+	Xiao and Tates 1995
CD-1 mice (inhalation)	Dominant lethality	-	Brinkworth et al. 1998
CAST/EiJ, NOD/LTj, A/J, WSB/EiJ, PWK/PhJ, 129S/SvlmJ, C57BL/6J mice (inhalation)	DNA adduct formation	+	Koturbash et al. 2011a
C57BL/6J mice (inhalation)	DNA adduct formation	+	Koturbash et al. 2011b
Humans (inhalation)	CA; SCE	+	Sram et al. 1998
Humans (inhalation)	CA; SCE	-	Lovreglio et al. 2006
Humans (inhalation)	*hprt* loci in peripheral lymphocytes	-	Hayes et al. 1996, 2000
Humans (inhalation)	*hprt* loci in peripheral lymphocytes	-	Tates et al. 1996
Humans (inhalation)	*hprt* loci in peripheral lymphocytes	-	Albertini et al. 2001, 2007; HEI 2003

Table 3-3. Genotoxicity of 1,3 Butadiene *In Vivo*

Species (test system)	End point	Results	Reference
Humans (inhalation)	*hprt* loci in peripheral lymphocytes	-	Liu et al. 2008
	hprt exon deletion	+	Liu et al. 2008
Humans (inhalation)	*hprt* loci in peripheral lymphocytes	+	Ward et al. 1994
Humans (inhalation)	*hprt* loci in peripheral lymphocytes	+	Abdel-Rahman et al. 2001, 2003, 2005; Ma et al. 2000; Ward et al. 1996, 2001
Humans (inhalation)	*hprt* loci in peripheral lymphocytes	+	Wickliffe et al. 2009
C3H mice (inhalation)	Induction of spermatid micronuclei	+	Tommasi et al. 1998
B6C3F1 mice (inhalation)	H- and K-*ras* mutation frequency	+	Sills et al. 2001
NMRI mice (inhalation)	Bone marrow: induction of micronuclei	+	Vodicka et al. 2006

– = negative result; + = positive result; AGT = average generation time; CA = chromosomal aberration; MI = mitotic index; MN = micronucleated cell; SCEs = sister chromatid exchange

low-exposure area. A significant correlation between *hprt* variant frequency and urinary levels of the 1,3-butadiene-specific metabolite, M1, was also found. No significant correlations between *hprt* variant frequency and age or employment length were found. A subsequent study of these workers reported 2.5-fold higher *hprt* mutation frequencies in workers exposed to airborne concentrations of 0.3 ppm 1,3-butadiene as compared to workers exposed to mean levels of 0.12 ppm (Ward et al. 1996), indicating good correlation between exposure and mutation frequency. Unlike the earlier study, no correlation between *hprt* variant frequency and urinary metabolite levels were found. A follow-up study of the southeast Texas SBR workers found a 3-fold increase in *hprt* mutation frequency in workers exposed to 1.7 ppm, compared to workers exposed to 0.07 ppm (Ward et al. 2001). A re-analysis of the blood samples from the Ward et al. (1996) study using a cloning assay, rather than the autoradiographic assay used in the Ward analyses, confirmed the significant difference in *hprt* variant frequency between high-exposure workers and the outside controls and found a significant difference in *hprt* mutation frequency between the groups (Ma et al. 2000). However, the investigators did not examine the possible association between 1,3-butadiene exposure level and mutation frequency. Neither Ma et al. (2000) nor Ward et al. (1994, 1996) provided demographic information on the outside control group, which consisted of workers in the Department of Preventive Medicine and Community Health at the University of Texas Medical Branch; thus, the appropriateness of this comparison group to the SBR workers cannot be evaluated. A more recent study of these SBR workers did not find a significant association between 1,3-butadiene exposure level and *hprt* variant frequency, after removal of an outlier (Wickliffe et al. 2009). The current 1,3-butadiene exposure levels of the 30 subjects examined were low with only six subjects having levels of >0.1 ppm. A significant association between employment length and *hprt* mutant frequency was found. Another study conducted by this group (Ammenheuser et al. 2001) at a different SBR facility found a 3-fold increase in *hprt* mutation frequency in 22 workers in the high-exposure group (mean 1,3-butadiene exposure level was 1.48 ppm) compared to low-exposure workers (mean exposure level of 0.15 ppm). Significant correlations between *hprt* variant frequency and 1,3-butadiene levels and urinary M1 levels were found. Abdel-Rahman et al. (2001, 2003, 2005) examined the association between polymorphisms, 1,3-butadiene exposure, and *hprt* variant frequency among workers at the two Texas SBR facilities. Individuals with a polymorphism for microsomal epoxide hydrolase (EH), an enzyme important for the hydrolysis of epoxide metabolites of 1,3-butadiene (see Section 3.4.3), exhibited a 3-fold higher *hprt* mutation frequency than workers without the polymorphism (Abdel-Rahman et al. 2001). Further, polymorphisms in the glutathione-S-transferase (another important enzyme in epoxide metabolite metabolism) genotypes GSTM1 or GSTT1 did not impact *hprt* mutation rates, but a combination of EH and GST polymorphism did result in an increase in *hprt* mutation frequency (Abdel-Rahman et al. 2001, 2003, 2005). Several studies that examined the possible association between

1,3-butadiene exposure and the frequency of chromosomal aberrations and/or sister chromatid exchanges among Texas 1,3-butadiene workers have not found significant associations (Au et al. 1995; Hallberg et al. 1997; Kelsey et al. 1995).

Unlike the results of Texas cohorts, studies of Chinese rubber production workers have not found alterations in *hprt* mutation frequency. No significant difference in *hprt* gene mutation frequency was observed in male and female Chinese polybutadiene rubber production workers exposed to an average of 1.0–3.5 ppm (median of 2.0 ppm) and unexposed controls (Hayes et al. 1996, 2000, 2001). Additionally, no exposure-related significant associations between *hprt* mutation frequency and 1,3-butadiene exposure (as assessed by exposure levels, urinary metabolite levels, or hemoglobin adducts) were found. Similarly, no significant alterations in glycophorin A variant frequencies were observed (Hayes et al. 2000). In another Chinese study, *hprt* mutation frequencies in petrochemical workers exposed to mean levels of 10 ppm were higher, but were not significantly different than unexposed controls, while the percentage of workers exhibiting *hprt* exon deletions (27%) was significantly higher than levels found in controls (13%) (Liu et al. 2008).

Several investigators have examined *hprt* mutation frequency in cohorts of 1,3-butadiene workers in the Czech Republic. Tates et al. (1996) did not find significant alterations in *hprt* mutation frequency among male workers from a 1,3-butadiene production plant exposed to a mean concentration of 1.76 ppm, as compared to unexposed workers at the plant. However, a significant increase in the percentage of lymphocytes with chromosomal aberrations was observed in the exposed workers; increases in DNA damage (as assessed using the comet assay) and micronuclei frequency were observed in exposed smokers, as compared to unexposed smokers (Šrám et al. 1998; Tates et al. 1996). A significant increase in the frequency of sister chromatid exchanges was also observed (Šrám et al. 1998). When the exposed workers and unexposed workers were subdivided based on glutathione-*S*-transferase polymorphism for M1 gene (GSTM1) and glutathione-*S*-transferase polymorphism for T1 gene (GSTT1) genotypes, a significant increase in the frequency of chromosomal aberrations were observed in exposed workers with the GSTM1-positive genotype, as compared to exposed workers with GSTM1-null genotype; no effects was observed for the GSTT1 genotype. Multifactorial analysis (accounting for 1,3-butadiene exposure, smoking, GSTM1, GSTT1, and age) showed a significant association between the frequency of chromosomal aberrations and the number of cells with a high frequency of sister chromatid exchanges (Šrám et al. 1998). However, when 1,3-butadiene exposure was evaluated using N-1-(2,3,4-trihydroxy-butyl)adenine adduct levels, there were no significant associations between chromosomal aberration frequency, micronuclei formation, or sister chromatid exchange (Zhao et al. 2001). In another study of

Czech 1,3-butadiene workers, no alterations in chromosome aberrations, sister chromatid exchanges, or micronuclei formation were observed in 1,3-butadiene production workers or workers in 1,3-butadiene polymer production (Sorsa et al. 1994). However, when workers were subdivided based on GSTM1 and GSTT1 genotypes, a significantly higher frequency of chromosomal aberrations were observed in 1,3-butadiene workers lacking the GSTT1 gene (Sorsa et al. 1996). In a larger-scale study of 24 workers at a 1,3-butadiene production facility (mean exposure level of 0.64 mg/m^3 [0.29 ppm]) and 34 workers at a polymerization facility (mean exposure level of 1.76 mg/m^3 [0.79 ppm]), no significant association between 1,3-butadiene exposure (as assessed using air concentrations, urinary metabolites, or hemoglobin adducts) and *hprt* mutation frequency (assessed using cloning assay) were found; no associations were found when workers divided by a number of genotypes including GSTM1 or GSTT1 (Albertini et al. 2001; HEI 2003). No significant alterations in the frequency of chromosomal aberrations or sister chromatid exchanges were found. In a follow-up study at the polymerization facility, male and female workers were examined. The mean 1,3-butadiene exposure levels were 0.397 mg/m^3 (0.18 ppm) and 0.808 mg/m^3 (0.36 ppm) in the females and males, respectively (Albertini et al. 2007). No significant associations between 1,3-butadiene exposure and *hprt* mutation frequency were found; similarly, there were no significant associations between exposure and sister chromatid exchanges or chromosomal aberrations.

In a cohort of workers at an Italian petrochemical plant exposed to very low levels of 1,3-butadiene (mean concentration of 0.0115 mg/m^3 [0.005 ppm]), no significant relationship between 1,3-butadiene exposure and alterations in the frequency of chromosomal aberrations or sister chromatid exchanges was observed Fustinoni et al. 2004; Lovreglio et al. 2006).

In summary, studies of workers at Texas 1,3-butadiene production facilities or SBR facilities have found significantly higher frequencies of *hprt* variants in the lymphocytes in men working in areas of the facility with high 1,3-butadiene exposure levels (Ammenheuser et al. 2001; Ma et al. 2000; Ward et al. 1996, 2001) However, no significant associations were found in Czech cohorts (Albertini et al. 2001, 2007; HEI 2003; Tates et al. 1996) or Chinese cohorts (Hayes et al. 1996, 2000, 2001). The reasons for dissimilar outcomes in lymphocyte *hprt* gene mutation frequency between the different cohorts are not clear, but may be the result of varying exposure levels, experimental techniques in exposures assessment (active vs. passive sampling) and mutation analysis (autoradiography vs. cloning *hprt* assays). The mean exposure levels in the Texas cohort studies tended to be higher than other cohorts; the mean levels in the Chinese cohort are elevated due to intermittent high exposures rather than a high TWA level. This is supported by a study conducted by Wickliffe et al. (2009) that did not find significant increases in *hprt*

frequency in a Texas cohort with low 1,3-butadiene exposure levels (only six subjects were exposed to levels >0.1 ppm).

A number of rodent inhalation studies report genotoxic effects. Mice and rats exhibited increased *hprt* locus mutations in splenic T cells (Cochrane and Skopek 1993; Meng et al. 1999, 2000, 2004, 2007). Inhaled 1,3-butadiene also induce an increase in micronucleus induction in erythrocytes (Irons et al. 1986b; Jauhar et al. 1988; Tice et al. 1987; Vodicka et al. 2006), spermatocytes (Tommasi et al. 1998; Xiao and Tates 1995), and bone marrow cells (Autio et al. 1994), increased frequency of sister chromatid exchanges (Tice et al. 1987) and chromosomal aberration frequencies (Cunningham et al. 1986; Tice et al. 1987) in mice. Transgenic B6C3F1 mice exhibited an increased *lacZ*$^-$ mutant frequency in the lungs (Recio et al. 1992). Increased percentages of H- and K-*ras* proto-oncogene mutations were found in forestomach neoplasms from mice inhaling 1,3-butadiene for 2 years (83% in exposed mice compared to 24% in spontaneous neoplasms from controls) (Sills et al. 2001). Increases in N-7-(2,3,4-trihydroxybut-1-yl) guanine adduct formation in liver DNA were found in various mouse strains exposed to 1,3-butadiene (Koturbash et al. 2011a, 2011b); the increase DNA adduct formation was concentration-related (Koturbash et al. 2011b). No genotoxic effects (micronucleus induction, chromosomal aberrations, or sister chromatid exchanges) were found in bone marrow of rats or liver of mice exposed by inhalation to 1,3-butadiene (Autio et al. 1994; Cunningham et al. 1986; Recio et al. 1992).

In a dominant lethal study in which male CD-1 mice inhaled 1,3-butadiene for 5 days and were mated to nonexposed females, an increased number of dead implantations per pregnancy occurred at 200 and 1,000 ppm, but not at 5,000 ppm during the first 2 weeks postexposure (DOE/NTP 1988b). These results were considered to be inconclusive because of the lack of a strict dose-response relationship. Increased numbers of dead fetuses were also observed in offspring of CH3 males inhaling 130 ppm (Adler et al. 1998), but not in CD-1 mice exposed to 125 ppm (Brinkworth et al. 1998). Heritable spermatid chromosomal translocations occurred in F_1 offspring of male CH3 mice inhaling 1,3-butadiene (Adler et al. 1995a, 1998).

Although cytogenetic monitoring of 1,3-butadiene rubber workers for chromosomal aberrations revealed no or slight differences between exposed and control groups (Lovreglio et al. 2006; Sram et al. 1998; Zhou et al. 1986), 1,3-butadiene is clearly genotoxic in mice. As discussed in Section 3.4.3, species differences exist in the metabolism of 1,3-butadiene, and data suggest that humans may metabolize this compound at different metabolic rates than do rodents. If the genotoxic and clastogenic response of 1,3-butadiene requires activation to an active metabolite that is formed more slowly or deactivated more

rapidly in humans than in rats and mice, the genotoxicity observed in animals may only be observed after much higher exposures in humans. The data in humans are too limited, however, to rule out the possibility of a genotoxic potential in humans exposed to 1,3-butadiene.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

In human volunteers inhaling 2 ppm 1,3-butadiene for 20 minutes, the absorbed fraction varied from 18 to 74% (Lin et al. 2001). Neither sex nor age (30±8 years for males, 29±9 years for females) were factors in this variation. Fractional absorption in Asian volunteers was about 20% greater than in Caucasians, African-Americans, or Hispanics. Blood triglyceride levels may influence absorption, as blood:air partition coefficients increased 20–40% in humans having borderline higher triglyceride levels after ingestion of fat in the diet (Lin et al. 2002).

In male Sprague-Dawley rats and male B6C3F1 mice exposed to 20 ppm ^{14}C-radiolabeled 1,3-butadiene for 6 hours in a dynamic system, the total absorbed radioactivity, as estimated by the sum of ^{14}C in urine, feces, carcass, and expired air, was 2.2% in rats and 1.6% in mice (Swain et al. 2003). In close-chamber studies, the uptake of inhaled 1,3-butadiene in mice and rats was linear to 2,000 and 1,000 ppm, respectively, above which metabolism is saturated (Kohn and Melnick 2001). Absorption of 1,3-butadiene was demonstrated by measurements of the metabolite, 1,2-epoxy-3-butene (EB), in the test chamber (due to exhaled air) and measurement of 1,3-butadiene metabolites in blood of male Sprague-Dawley rats exposed 1–10,000 ppm and male B6C3F1 mice exposed to 1–6,000 ppm for 6–8 hours in closed chambers (Filser et al. 2007). In rats, EB concentrations in the test chamber reached a plateau at all exposure concentrations. In mice, chamber concentrations of EB were higher than for rats; EB levels reached a plateau at exposure concentrations up to 1,000 ppm, but no plateau was observed at exposure concentrations of 2,000–6,000 ppm. The study authors suggest that this concentration-dependence is due to "breakdown" of hepatic glutathione-S-transferase mediated 1,3-butadiene conjugation. Filsner et al. (2007) did not report an absorption fraction for either species. Absorption of 1,3-butadiene was also demonstrated by measurement of metabolites (butadiene monoepoxide and butadiene diepoxide) in blood and tissues of male Sprague-Dawley rats and male B6C3F1 mice exposed (nose only) to 62.5 ppm 1,3-butadiene for 2 or 4 hours (Thornton-Manning et al. 1995a). Similar results were observed in male and female rats exposed (nose only) to 62.5 ppm 1,3-butadiene for 6 hours (Thornton-Manning et al.

1995b). The distribution coefficient for 1,3-butadiene between rabbit blood and air was 0.603 *in vitro* and 0.654 *in vivo*, suggesting simple passive diffusion of the gas from the alveoli to the blood (Carpenter et al. 1944). After 9 minutes of exposure of rabbits to 250,000 ppm, the concentration of 1,3-butadiene was 0.26 mg/mL in the femoral artery and 0.18 mg/mL in the femoral vein. Pulmonary absorption, therefore, appears to be rapid. Distribution studies in rats and mice following inhalation exposure to 1,3-butadiene indicate that it is absorbed from the lungs in these species as well (see Section 3.4.2.1). When *Macaca fascicularis* monkeys were exposed to radioactively labeled 1,3-butadiene, the uptake was calculated as 16.40 µmol/hour/10 ppm of inhaled and 3.20 µmol/hour/10 ppm of retained 1,3-butadiene (Dahl et al. 1990).

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals after oral exposure to 1,3-butadiene.

3.4.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to 1,3-butadiene.

3.4.2 Distribution

In vitro measurements of tissue:blood equilibrium partition coefficients suggest that 1,3-butadiene distributes to a variety of tissues. Partition coefficients in humans were highest in fat (18.4) and were similar in well- and poorly-perfused tissues (0.69 and 0.72, respectively) (Brochot et al. 2007). In rats, partition coefficients were highest for fat (21.9), similar for liver, kidney, muscle, and spleen (0.87–0.94), and lowest in brain (0.43) (Johanson and Filser 1993).

3.4.2.1 Inhalation Exposure

In volunteers inhaling 2 ppm 1,3-butadiene for 20 minutes, blood levels approached equilibrium by 5 minutes (Smith et al. 2001). In mice and rats inhaling up to 625 ppm 1,3-butadiene, equilibrium in blood concentrations was reached by 2 hours, with blood levels in mice being three- to 4-fold higher than in rats at all times (Himmelstein et al. 1994). The distribution of 1,3-butadiene in several tissues in rats was measured following a 1-hour inhalation exposure to 129,000 ppm (Shugaev 1969). Perinephric fat

contained 152 mg 1,3-butadiene/100 cc tissue, compared to levels of 36–51 mg 1,3-butadiene/100 mL in the brain, liver, septum, and kidney.

Species differences in the distribution of inhaled 1,3-butadiene were studied in Sprague-Dawley rats and B6C3F1 mice (Bond et al. 1986, 1987). When normalized for amount of inhaled ^{14}C-1,3-butadiene, molar tissue concentrations of radioactive material at 1 hour postexposure were 17-fold (thyroid) to 80-fold higher (lung) in mice than in rats. In blood, the normalized radioactivity concentration was 57-fold higher in mice than rats, while 110- to 120-fold more radioactivity was found in mouse intestine than in rat intestine.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals after oral exposure to 1,3-butadiene.

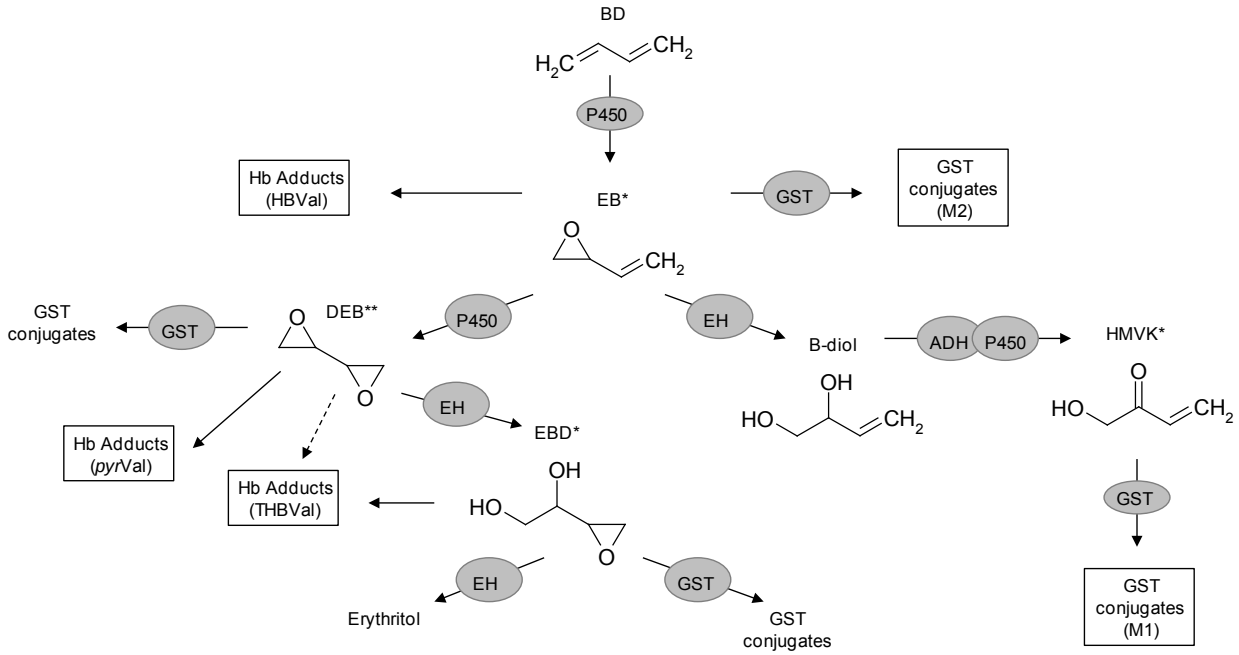
3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to 1,3-butadiene.

3.4.3 Metabolism

1,3-Butadiene is metabolized by oxidation, hydrolysis, and conjugation reactions, with oxidation and hydrolysis reactions leading to the formation of several reactive epoxide intermediates (Figure 3-2). Of the reactive intermediates formed, EB (formed by oxidation of 1,3-butadiene), 1,2:3,4-diepoxybutane (DEB; formed by oxidation of EB), and 1,2-dihydroxy-3,4-epoxybutane (EBD; formed by hydrolysis reactions of DEB) are reactive electrophilic compounds. Metabolism of 1,3-butadiene appears to follow the same enzymatic pathways in all species, including humans, with production of the same reactive intermediates. However, important species differences exist in the rates of formation and detoxification of reactive metabolites (Kirman et al. 2010a). As a result, rodents, particularly mice, have much higher tissue levels of reactive metabolites than nonhuman primates and humans. Evidence for species differences in metabolism of 1,3-butadiene is available from *in vitro* studies, studies using isolated perfused livers, and *in vivo* studies measuring tissue and urine metabolite levels and blood hemoglobin adduct levels. Metabolism of 1,3-butadiene exhibits nonlinear kinetics (Kirman et al. 2010a), with both dose- and exposure duration-dependent effects. Several processes have been proposed as sources of

Figure 3-2. Metabolism of 1,3-Butadiene



□ = boxes indicate biomarkers of exposure that have been measured in exposed workers (Albertini et al. 2003);
* = monofunctional alkylating agent; ** = bifunctional alkylating agent; ADH = alcohol dehydrogenase;
B-diol = butanediol; BD = 1,3-butadiene; DEB = diepoxybutane; EB = epoxybutene; EBD = epoxybutane diol;
EH = epoxide hydrolase; GST = glutathione S-transferase; HBVal = *N*-(2-hydroxy-3-butenyl)-valine;
HMVK = hydroxymethylvinyl ketone; M1 = 1,2-dihydroxy-4-(*N*-acetylcysteinyl)-butane (urinary metabolite);
M2 = 1-(*N*-acetylcysteinyl)-2-hydroxy-3-butene (urinary metabolite); P450 = cytochrome P450;
*pyr*Val = *N,N*-(2,3-dihydroxy-1,4-butadiyl)-valine; THBVal = *N*-(2,3,4-trihydroxybutyl)-valine

Source: Kirman et al. 2010

nonlinear kinetics; these include inhibition, induction, and saturation of various metabolizing enzymes and depletion of glutathione.

The metabolism of 1,3-butadiene has been observed in the liver, lung, and kidneys. The liver is the predominant site of 1,3-butadiene metabolism (Elfarra et al. 2001; Schmidt and Loeser 1985, 1986). 1,3-Butadiene is initially oxidized (Figure 3-2) by cytochrome P450 (CYP) to 2-butenal or EB (Bolt et al. 1983; Csanady et al. 1992; Duescher and Elfarra 1994; Himmelstein et al. 1994, 1995; Kirman et al. 2010; Malvoisin and Roberfroid 1982; Malvoisin et al. 1979; Thornton-Manning et al. 1995b, 1997). Metabolism of EB is mediated by three competing oxidative, hydrolytic, or conjugation pathways. The flux of 1,3-butadiene through the various pathways is concentration- and species-dependent. Successive oxidation steps of EB result in DEB and 3,4-epoxy-1,2-diol (EBdiol). EB can also be conjugated to glutathione by glutathione-S-transferase (GST) to form 1-glutathionyl-3-buten-2-ol, or can be hydrolized via epoxide hydrolase (EH) to 3-butene-1,2-diol (BDdiol). BDdiol is metabolized via CYP or aldehyde dehydrogenase (ADH) to the ketone 1-hydrozy-3-buten-2-one (hydroxymethylvinyl ketone, or HMVK) or EBdiol. GST can conjugate glutathione to HMVK and EBdiol to form 4-glutathionyl-1-hydroxy-2-butanone and 4-glutathionylbutane-1,2,3-triol. Several isoforms of CYP have been implicated in the oxidative metabolism of 1,3-butadiene and resulting epoxides in various tissues. In human liver microsomes, CYP2E1 dominates metabolism at low concentrations (i.e., 0.16 mM), while CYP2A6 dominates at higher concentrations (i.e., 4.4 mM) (Elfarra et al. 1996). In mice, CYP2E1 and 2A5 are active in 1,3-butadiene oxidation in lung and liver microsomes, but CYP4B1 dominates metabolism in the kidneys (Elfarra et al. 2001).

Examination of blood levels of 1,3-butadiene metabolites in male Sprague-Dawley rats exposed to 1–10,000 ppm and male B6C3F1 mice exposed to 1–6,000 ppm for 6–8 hours in closed chambers indicates species differences in the predominance of metabolic pathways (Filsner et al. 2007). In rats and mice, EB, EBD, and 3-butene-1,2-diol concentrations in blood increased with increasing exposure concentrations. Ratios of mouse:rat EB blood levels ranged from 2.0 to 8.6 over 1,3-butadiene exposure concentrations of 1–1,250 ppm. DEB was detected in blood of mice, but not in rats. Similar results were observed in male Sprague-Dawley rats and male B6C3F1 mice exposed (nose only) to 62.5, 625, or 1,250 ppm 1,3-butadiene for 6 hours; DEB was detected in mouse, but not rat, blood, and higher levels of butadiene monoepoxide were present in mouse blood, compared to rat blood (Himmelstein et al. 1994). Results of these studies are consistent with enhanced formation and/or lower metabolism of DEB in mice compared to rats. Differences also were noted between rodents and monkeys in 1,3-butadiene metabolism (Dahl et al. 1990; Sun et al. 1989a). At 10 ppm, blood levels of EB, DEB, and EBdiol were

lower in monkeys inhaling 10 ppm than in rodents. The difference was not so great at 8,000 ppm (Sun et al. 1989a). Similar exposures of 10 ppm 1,3-butadiene resulted in blood concentrations of total 1,3-butadiene metabolites in monkeys that were about 5–50 times lower than in mice and about 4–14 times lower than in rats (Dahl et al. 1991). The results indicated possible lower susceptibility to toxic effects of low levels of 1,3-butadiene in primates.

Species differences in metabolism are also supported by results of studies examining tissue levels of metabolites (Filser et a;. 2007; Himmelstein et al. 1995; Thorton-Manning et al. 1995a, 1995b). Comparison of butadiene epoxide levels in livers and lungs of male Sprague-Dawley rats and male B6C3F1 exposed (nose only) to 62.5, 625, 1,250, or 8,000 (rats only) ppm 1,3-butadiene shows higher levels of butadiene monoepoxide in mice compared to rats, and the presence of butadiene diepoxide in mice, but not rats (Himmelstein et al. 1995). In male Sprague-Dawley rats and male B6C3F1 mice exposed to 62.5 ppm 1,3-butadiene for 4 hours, tissue levels of butadiene monoepoxide were higher in tissues (blood, heart, lung, liver, fat, spleen, and bone marrow) of mice compared to rats, with mouse:rat ratios ranging from 3.0 (heart) to 11.5 (bone marrow); butadiene diepoxide was not detected in lung or liver of rats (Thorton-Manning et al. 1995a). In mice, butadiene diepoxide levels were similar to monoepoxide levels in blood, heart, thymus and bone marrow; diepoxide levels in mouse lung, liver, and spleen were higher than monoepoxide levels, but were lower in fat. Butadiene diepoxide levels in rats were very low compared to levels in mice, and diepoxide was not detected in liver or bone marrow. Comparison of butadiene epoxide levels in tissues of male and female Sprague-Dawley rats exposed to 1,3-buradiene for 6 hours (nose only) suggests gender differences in metabolism (Thorton-Manning et al. 1995b). Butadiene monoepoxide levels in lung were approximately 5-fold higher in males compared to females; whereas similar monoepoxide levels for males and females were observed for blood, femur, and fat.

Results of studies using isolated perfused livers provide additional evidence of species differences in metabolism of 1,3-butadiene. Following single pass, isolated perfusion of livers from male Sprague-Dawley rats and male B6C3F1 mice with 1,3-butadiene (at concentrations that approached saturation of 1,3-butadiene metabolism), differences were observed in 1,3-butadiene metabolites in liver effluent (Filser et al. 2001). In mice, three epoxides (EB, DEB, and EBD) and 3-butane-1,2-diol (B-diol) were detected, whereas only EB and B-diol were detected in effluent from rat livers. Furthermore, the concentration of EB in effluent from rat livers was approximately 8.5-fold less than that in effluent from mouse livers. Additional species differences were observed in a study evaluating single-pass perfusion of the 1,3-butadiene metabolites, EB, DEB and B-diol (Filser et al. 2010). For perfusion with EB, EBD,

DEB, and B-diol were formed in rats and mice, with an approximately 4-fold higher percentage of DEB in mice compared to rats. The major metabolite of DEB in rats and mice was EBD. For perfusion with B-diol, EBD was detected in effluent of rats, but not in mice. Results of studies using hepatic microsomes from mice and rats indicate differences in stereochemistry of 1,3-butadiene metabolites (Nieusma et al. 1997). Mouse microsomes form more (*S*)-EB than (*R*)-EB; rat microsomes initially formed more (*S*)-EB than (*R*)-EB, although the *S*:*R* fell below 1.0 as incubation time increased to 30 minutes. For DEB formation, mice microsomes formed more DEB when starting with (*S*)-EB compared to when starting with (*R*)-EB; the opposite was observed with rat microsomes.

In vitro studies indicate that mouse lung and liver have a higher capacity than other species, including humans, to oxidize 1,3-butadiene to EB and DEB, but have much less ability to detoxify the epoxides via the EH pathway (Jackson et al. 2000b). Female mouse tissue homogenates resulted in higher EB generation than in males or in rat, human, or monkey tissues, while human and monkey tissues hydrolyzed the epoxides to diols approximately 20-fold more extensively than rodents (Schmidt and Loeser 1985, 1986). In studies of liver microsomes, mice had intrinsic clearance (V_{max}/K_m) values of 57.5 and 0.77 $minute^{-1}$ for oxidation of 1,3-butadiene to EB and EB to DEB, respectively. These values are 3–4-fold higher than the respective rat values of 1,637 and 0.21 $minute^{-1}$ (Elfarra et al. 2001). Conversely, intrinsic clearance via EH-mediated hydrolysis of EB was 34.4 $minute^{-1}$ in rats, compared to 12.4 $minute^{-1}$ in mice. Clearance by EB conjugation with GSH was similar (21.0 and 22.0 $minute^{-1}$) in both species. These *in vitro* findings comport with metabolic differences observed between rats and mice after inhalation exposure to EB (Kreiling et al. 1987; Laib et al. 1990). A limited rate of EB removal and its subsequent accumulation was observed in mice at 500 ppm exposure, but not in rats at exposures up to 5,000 ppm. This may partially account for the differing levels of toxicity and carcinogenicity between rats and mice in long-term studies. For additional information, see Section 3.5 (Mechanisms of Action).

Based on evaluation of hemoglobin adduct biomarkers (adducts formed by interaction of 1,3-butadiene metabolites with hemoglobin), mice appear to have higher DEB levels than rats and much higher levels than humans (Swenberg et al. 2007). Analysis of hemoglobin adducts in mice and rats exposed to 1,3-butadiene by inhalation show much higher levels of the hemoglobin adducts, *pyr*-Val and THB-Val (formed by interaction of DEB with hemoglobin), in mice than in rats (Boysen et al. 2004). Results are consistent with results of studies showing higher levels of DEB in tissues of mice compared to rats. In polymerization workers exposed to 0.81 ppm 1,3-butadiene, THB-Val was the predominant hemoglobin adduct, comprising 99.6% of the total; the mean percent of HB-Val was 0.33% and the mean percent of *pyr*-Val was 0.05% (Boysen et al. 2012). In monomer workers exposed to lower concentrations of

1,3-butadiene (0.29 ppm), lower levels of HB-Val (0.26%) and higher levels of *pyr*-Val (0.11%) were found; the decrease in *pyr*-Val levels was significantly related to the increasing 1,3-butadiene concentrations. The lower percentage of *pyr*-Val formed in the workers exposed to higher 1,3-butadiene levels may be suggestive of saturation of the formation of *pyr*-Val in humans (Boysen et al. 2012).

As noted in the introduction to Section 3.4.3, metabolism of 1,3-butadiene exhibits nonlinear kinetics (Kirman et al. 2010a), with both dose- and exposure duration-dependent effects. Glutathione deletion and saturable kinetics have been proposed as possible sources of nonlinear kinetics. Studies evaluating effects of hepatic glutathione levels show that gluthione depletion exhibited concentration-dependence and was greater in mice than in rats (Deutschman and Laib, 1989; Kreiling et al. 1988). Glutathione depletion was also observed in livers and lungs of rats and mice exposed to 1,3-butadiene, with more extensive depletion in mice than in rats (Himmelstein et al. 1995). Regarding saturable kinetics, blood levels of EB reached a plateau in rats, but not mice (Filser et al. 2007). The study authors suggested that the results are consistent with competitive inhibition of CYP450 isozymes.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

The monoepoxide metabolite, EB, can be conjugated to glutathione by GST to form monohydroxybutenylmercaptic acid (MHBMA, or M2), a mixture of N-acetyl-S-([1-hydroxymethyl]-2-propenyl)cysteine and N-acetyl-S-([2-hydroxymethyl]-3-propenyl)cysteine. EBdiol, formed by hydrolysis of EB, may also be conjugated by GST to glutathione to form N-acetyl-S-(3,4-dihydroxy-butyl)cysteine (DHBMA, or M1). Both mercaptic acids are excreted in the urine (Boogaard et al. 2001a; McDonald et al. 2004). These excretion products have been used as biomarkers of 1,3-butadiene exposures in both environmental and occupational settings (Albertini et al. 2001, 2007; Ammenheuser et al. 2001; Boogaard et al. 2001a) (see Section 3.8). The relative abundance of MHBMA and DHBMA in urine indicates the flux of EB through the competing GST and EH metabolic pathways. In humans, >97% of urinary mercaptic acid measured following 1,3-butadiene inhalation is DHBMA, indicating that most EB proceeds to hydrolysis via EH rather than to formation of the diepoxide (Henderson et al. 1996). Albertini et al. (2007) showed that women excrete lower levels of both mercaptic acids than men per unit of 1,3-butadiene exposure; however, they maintain the ratio of M1 and M2, suggesting sex differences in metabolic activity, but not pathway flux.

In rats exposed to 1,3-butadiene, 1,2-epoxybutene-3 and acetone were exhaled as suspected metabolites of the administered compound (Bolt et al. 1983). The pharmacokinetic profile of inhaled 1,3-butadiene was studied in mice (Kreiling et al. 1986b) and in rats (Bolt et al. 1984; Filser and Bolt 1984). Following exposure of mice and rats to ^{14}C-1,3-butadiene, the elimination of radioactivity was rapid, and 77–99% of the initial tissue amount was eliminated with half-lives of between 2 and 10 hours (Bond et al. 1987). At concentrations of approximately ≤1,000 ppm, the elimination of 1,3-butadiene followed first-order kinetics in both species. The first-order metabolic clearance of inhaled 1,3-butadiene per kg body weight was 4,500 mL/hour for rats (Laib et al. 1988) and 7,300 mL/hour for mice (Kreiling et al. 1986b). The maximal metabolic elimination rate was calculated as 220 μmol/hour/kg for rats (Laib et al. 1988) and 400 μmol/hour/kg for mice (Kreiling et al. 1986b). With increasing concentrations of ^{14}C-1,3-butadiene, exhalation of radiolabeled carbon was a major pathway for elimination of ^{14}C in mice and rats (Bond et al. 1986). Similar results were observed in mice and rats following inhalation of 62.5 ppm 1,3-butadiene for 6 hours (Himmelstein et al. 1996). Blood 1,3-butadiene concentrations in mice fell from about 3 μM at the end of exposure to 0.03 μM 15 minutes later. Rat elimination of 1,3-butadiene from blood was slower, falling from a post-exposure maximum of about 1.5–0.1 μM 30 minutes later.

About 2% of the total inhaled amount of 1,3-butadiene was excreted as metabolites in Cynomolgus monkeys (Sun et al. 1989a). Carbon dioxide was the major exhalation product at 10 ppm, while epoxy-metabolites (specific compounds not determined) were predominant in exhaled breath at 300 and 8,000 ppm. Urinary excretion of total metabolites was not influenced by exposure levels. In *Macaca fascicularis* monkeys, about 39% of metabolite radioactivity (specific compounds not determined) were eliminated in the urine, 0.8% in feces, and 56% were exhaled as carbon dioxide during the first 70 hours postexposure (Dahl et al. 1990).

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans or animals after oral exposure to 1,3-butadiene.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to 1,3-butadiene.

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

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

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

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

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

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

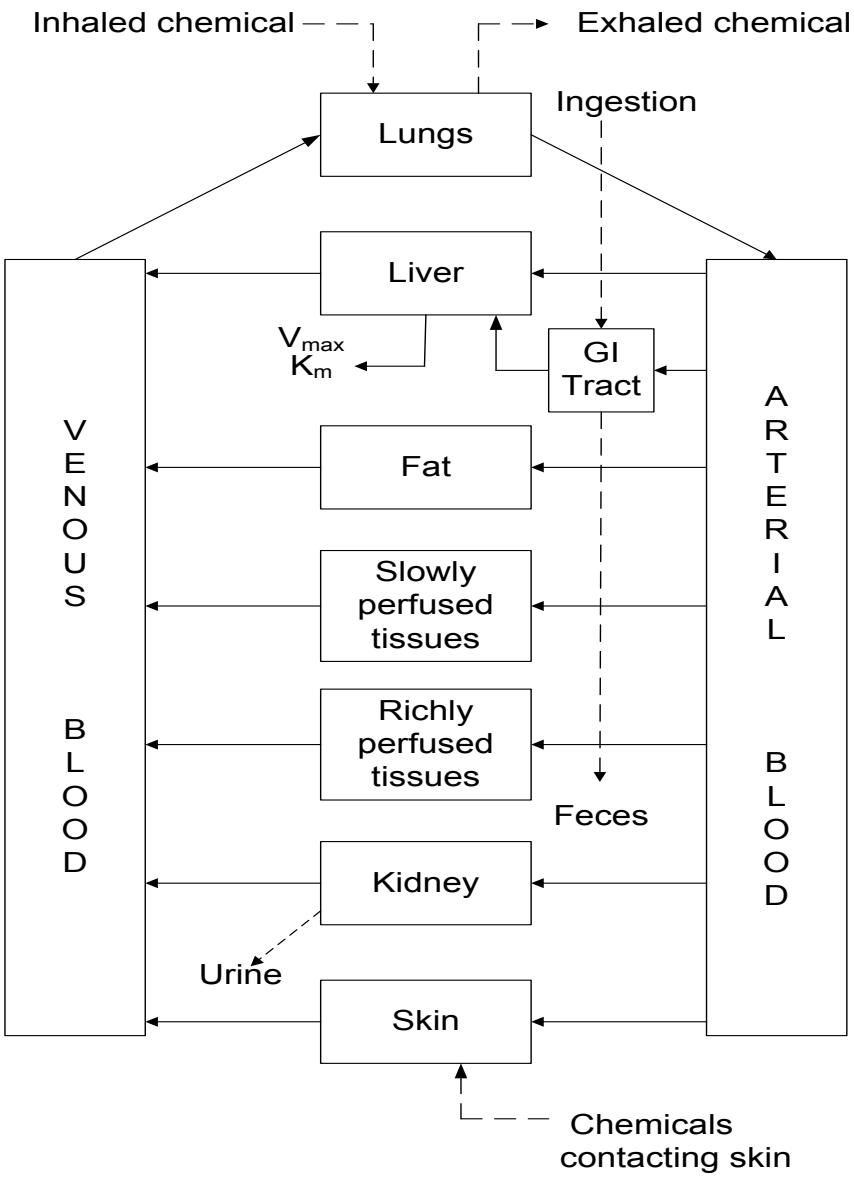
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in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

Literature on PBPK modeling of 1,3-butadiene is extensive (Beaudouin et al. 2010; Bois et al. 1999; Bond et al. 1996; Brochot et al. 2007; Csanady et al. 1996; Evelo et al. 1993; Filser et al. 1993; Johanson and Filser 1993, 1996; Kohn 1997; Kohn and Melnick 1993, 1996, 2000, 2001; Leavens and Bond 1996, Péry and Bois 2009; Seilken et al. 1996; Smith et al. 2001; Sweeney et al. 1996, 1997, 2001). Models have been developed to simulate 1,3-butadiene kinetics in mice (Bond et al. 1996; Csanady et al. 1996; Johanson and Filser 1993, 1996; Kohn and Melnick 1993, 1996, 2000, 2001; Leavens and Bond 1996; Sweeney et al. 1996, 1997, 2001), rats (Bond et al. 1996; Csanady et al. 1996; Johanson and Filser 1993, 1996; Kohn and Melnick 1993, 1996, 2000, 2001; Sweeney et al. 1996, 1997, 2001), and humans (Beaudouin et al. 2010; Bond et al. 1996; Brochot et al. 2007; Csanady et al. 1996; Evelo et al. 1993; Johanson and Filser 1996; Péry and Bois 2009). Model structures differ with respect to the number of physiological compartments simulated, the extent to which secondary and tertiary metabolites are simulated, and in which tissue compartments metabolism is assumed to occur. Selected examples are described in greater detail in the sections that follow.

Johanson and Filser 1996

Description of the Model. The Johanson and Filser model (Filser et al. 1993; Johanson and Filser 1993, 1996) model simulates absorption and disposition of 1,3-butadiene and the metabolite, 3,4-epoxy-1-butene, in the mouse, rat, and human. The hepatic conjugation of 3,4-epoxy-1-butene to GSH is also simulated. Tissue compartments include the blood/lung, liver, fat, and muscle/richly-perfused tissues.

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



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

Source: Adapted from Krishnan and Andersen 1994

Model parameters are presented in Table 3-4. Both the exchange of 1,3-butadiene and 3,4-epoxy-1-butene between blood and tissue or lung air is assumed to be first-order and flow-limited. *In vitro* derivation of tissue:air and tissue:blood partition coefficients was performed by the model authors and reported in the study. Michaelis-Menten expressions were included for 1,3-butadiene oxidation, 3,4-epoxy-1-butene hydrolysis, and 3,4-epoxy-1-butene conjugation to GSH, all occurring in the liver compartment. Values for physiological (alveolar, pulmonary, and tissue perfusion rates, organ weights) and metabolic parameters (V_{max}, K_m, and GSH content and elimination rates) were taken from the literature, except for the affinity constant (K_m) for 1,3-butadiene oxidation, which was fit to chamber air 1,3-butadiene timecourse data from rat and mouse closed chamber experiments. Elimination of 1,3-butadiene and 3,4-epoxy-1-butene was represented as either metabolism or as exchange passage back to the lung air.

Risk Assessment. This model has not been used in risk assessment. The model predicts that steady-state blood concentrations of 3,4-epoxy-1-butene resulting from continuous inhalation exposures to 1,3-butadiene would be higher in mice compared to rats or humans. At non-saturating conditions (e.g., exposures <1,000 ppm), the ratio of blood 3,4-epoxy-1-butene concentrations predicted from the model were: 1.6:1.0:0.3 for mouse:rat:human (Johanson and Filser 1996).

Validation of the Model. The K_m for 1,3-butadiene oxidation and 3,4-epoxy-1-butene hydrolysis were the only parameters optimized against close-chamber gas uptake data for 1,3-butadiene or 3,4-epoxy-1-butene (1,000–5,000 ppm) in rats (Filser and Bolt 1984) and mice (Kreiling et al. 1987). Model predictions were evaluated against the concentration of 3,4-epoxy-1-butene appearing in the chambers (due to metabolism and exhalation from the animals) during the 1,3-butadiene exposures, and were found to predict 3,4-epoxy-1-butene levels that were similar to observations.

Target Tissues. The model simulates concentrations of 1,3-butadiene and 3,4-epoxy-1-butene in liver, a target tissue for 1,3-butadiene metabolites, as well as in blood, fat, and a lumped compartment for muscle and richly-perfused tissues.

Species Extrapolation. The model has been developed for simulations of rats, mice, and humans. Extrapolation to other species would require species-specific physiological and metabolism parameter values and blood-tissue partition coefficients.

Table 3-4. Physiological and Chemical Parameters Used in the Johanson and Filser (1993) PBPK Model for 1,3-Butadiene

		Mouse	Rat
Physiological data			
Body weight (bw) (g)	Standard animal	25	250
	Simulations	27.5	157.5–217.5
Alveolar ventilation (mL/minute)	Standard animal	15	70.2
	Simulations	proportional to $bw^{2/3}$	proportional to $bw^{2/3}$
Cardiac output	Standard animal	17	83
	Simulations	proportional to $bw^{2/3}$	proportional to $bw^{2/3}$
Blood flows (percent of cardiac output)	Muscle and vessel-rich group (VRG)	66	66
	Fat	9	9
	Liver	25	25
Compartment volumes[a] (percent of body weight)	Lung and arterial	1	1
	Muscle and VRG	75	80
	Fat	10	7
	Liver	5.5	4
Tissue:air partition coefficients			
Butadiene	Lung and arterial, muscle and VRG, liver	0.76	0.76
	Fat	21.9	21.9
	Blood	3.03	3.03
Epoxybutene	Lung and arterial, muscle and VRG, liver	58.9	58.9
	Fat	155	155
	Blood	83.4	83.4
	Water	43.0	43.0
Metabolic constants			
Butadiene oxidation	Microsomal protein (mg/g liver)	30	30
	V_{max} (nmol·minute^{-1}·mg^{-1})	3.22	2.17
	K_m (µmol/L air)	5	5
Epoxybutene hydrolysis	Microsomal protein (mg/g liver)	30	30
	V_{max} (nmol·minute^{-1}·mg^{-1})	19	17
	Apparent K_m (mmol/L)	1.5	0.7
	Intrinsic K_m (percent of apparent K_m)	20%	20%
Epoxybutene conjugation	Cytosolic protein (mg/g liver)	95	95
	V_{max}/K_m of epoxybutene (µL·minute^{-1}·mg^{-1})	15	11
	K_m towards epoxybutene (mmol/L)	100	100
	K_m towards glutathione (mmol/L)	0.1	0.1
Glutathione kinetics	Initial steady-state concentration (mmol/L)	5.5	4.2
	Elimination rate constant (hour^{-1})	0.15	0.15

[a]Density was set to 1 for all organs

Source: Johanson and Filser 1993 (although simulations from a human model were reported in Johanson and Filser 1996, parameter values were not reported)

High-low Dose Extrapolation. The model has been evaluated for simulating inhalation exposures in mice and rats ranging from 500 to 5,000 ppm.

Interroute Extrapolation. The model simulates inhalation exposures only and would require additional parameterization to simulate exposures by other routes.

Strengths and Limitations. Strengths of the model are that it simulates disposition and clearance of inhaled 1,3-butadiene, as well as production and clearance of 3,4-epoxy-1-butene, the major oxidative metabolite formed in rodents. Limitations include: (1) the model has not been evaluated for inhalation exposures below 500 ppm; (2) the model does not simulate the appearance and disposition of other metabolites, such as the diepoxide, diols, and GSH-conjugate products eliminated in the urine; and (3) the model does not simulate 1,3-butadiene disposition in humans.

Kohn and Melnick 2001

Description of the Model. The Kohn and Melnick model (Kohn and Melnick 1993, 1996, 2000, 2001) simulates absorption of 1,3-butadiene and the disposition of 1,3-butadiene and the metabolite, 3,4-epoxy-1-butene, in the mouse and rat. Model parameters are presented in Tables 3-5, 3-6, and 3-7. The body is represented by discrete compartments for venous and arterial blood, lung, liver, kidney, fat, the gastrointestinal tract, and lumped compartments for richly- and poorly perfused tissues (viscera and muscle, respectively). Values for physiological flow rates, tissue volumes, and tissue:blood partition coefficients were taken from the literature. 1,3-Butadiene is eliminated by exhalation to lung air or oxidative metabolism to 3,4-epoxy-1-butene and its oxidation metabolites (3,4-epoxy-1-butene, DEB, 3,4-epoxy-1,2-diol, 3-butene-1,2-diol) and glutathione conjugates. All of these pathways are described as saturable Michaelis-Menten processes, with V_{max} and K_m values optimized against published closed-chamber 1,3-butadiene and 3,4-epoxy-1-butene uptake data (Bolt et al. 1984; Filser and Bolt 1984; Kreiling et al. 1986b, 1987). Epoxide hydrolysis was modeled such that dissociation of the diepoxide from P450 in the microsome is followed by preferential binding of the epoxide hydrolase, replicating the so-called privileged access model for epoxide hydrolysis. The model simulates production and utilization of glutathione in kidney, liver, and lung, with the assumption that glutathione production is limited by availability of cysteine for the first step in glutathione synthesis (γ-glutamylcysteine synthetase).

Risk Assessment. This model has not been used in risk assessment.

Table 3-5. Physiological Parameter Values Used in the Kohn and Melnick (2001) PBPK Model for 1,3-Butadiene

	Mouse (percent)	Rat (percent)
Tissue compartment volumes, percent body weight		
Liver	5.5	3.7
Lung	0.6	0.52
Alveolar	0.5	0.515
Kidney	1.67	1.48
Gastrointestinal tract	7.5	7.5
Viscera	3.93	14.3
Fat	6	7
Muscle and skin	64.5	54.2
Blood	6	5.4
Capillary blood volume, percent tissue volume		
Liver	11	13.8
Lung	11	18
Kidney	10.2	16
Gastrointestinal tract	2.9	2.65
Viscera	7.1	7.1
Fat	3	2
Muscle and skin	1.3	2
Blood flow rate, percent cardiac output		
Liver (hepatic artery only)	4.4	3.9
Kidney	16.3	13.3
Gastrointestinal tract	18.1	18.1
Viscera	22.4	24.8
Fat	5	6.5
Muscle and skin	33.8	33.4

Source: Kohn and Melnick 2001

Table 3-6. Chemical Partition Coefficients Parameter Values Used in the Kohn and Melnick (2001) PBPK Model for 1,3-Butadiene

	Butadiene	Epoxybutane	Butenediol	Epoxybutanediol	Diepoxybutane
Blood:air	1.95	56.8	–	–	–
Liver	0.595	0.984	1.04	0.903	1.41
Lung	0.615	0.977	1.107	0.958	1.41
Kidney	0.472	0.842	0.962	0.833	1.54
Gastrointestinal tract	0.446	0.908	1.22	1.06	1.41
Viscera	0.446	0.908	1.22	1.06	1.41
Fat	10.8	2.25	0.573	0.496	2.19
Muscle and skin	0.564	0.736	1.139	0.986	1.82

Source: Kohn and Melnick 2001

Table 3-7. Chemical Metabolism Parameter Values Used in the Kohn and Melnick (2001) PBPK Model for 1,3-Butadiene[a]

	Liver	Lung	Kidney
Butadiene metabolism			
V_{max}^{P450}	155, **130**	139, **9.6**	1,430, **30**
K_m^{P450}	0.002, **0.00375**	0.00501, **0.00775**	0.00501, **0.00216**
Epoxybutene metabolism			
V_{max}^{P450}	45.1, **24.3**	*10.2*, ***9.84***	*48.6*, ***12.6***
K_m^{P450}	0.0156, **0.145**	0.0156, **0.145**	0.0156, **0.145**
V_m^{EH}	347, **584**	34.8, **42.8**	*113*, ***14.7***
K_m^{EH}	1.59, **0.26**	1.59, **0.7**	1.59, **0.7**
V_{max}^{GST}	6,420, **4,260**	720, **196**	960, **494**
Adjusted K_{mx}^{GST}	3.59, **2.59**	3.59, **4.94**	3.59, **4.39**
Butenediol metabolism			
V_{max}^{P450}	*16.3*, *67.1*	*1.0*, *31.5*	*1.0*, ***85.0***
K_m^{P450}	0.0156, **0.145**	0.0156, **0.145**	0.0156, **0.145**
V_{max}^{GST}	*3,480*, *1,230*	*491*, *276*	*1,070*, ***658***
K_{mx}^{GST}	34, **34**	34, **34**	34, **34**
Epoxybutanediol metabolism			
V_{max}^{EH}	*363*, *1,150*	*69.5*, **169**	*10.0*, ***152***
K_m^{EH}	8.1, **2.76**	7.5, **7.1**	7.5, **7.1**
V_{max}^{GST}	*2,260*, **271**	*50.0*, **100**	*50.0*, ***138***
K_{mx}^{GST}	6.40, **4.17**	6.40, **4.17**	6.40, **4.17**
Diepoxybutane metabolism			
V_{max}^{EH}	1,920, **3,170**	10.0, **1,160**	*35.2*, ***1,000***
K_m^{EH}	8.1, **2.76**	7.5, **7.1**	7.5, **7.1**
V_{max}^{GST}	9,720, **1,940**	*100*, *100*	*100*, *100*
Adjusted K_{mx}^{GST}	6.40, **4.17**	6.40, **4.17**	6.40, **4.17**
Cysteine metabolism			
Tissue cysteine	0.193, **0.195**	0.171, **0.127**	0.280, **0.326**
$V_{max}^{\gamma\text{-GCS}}$	420, **396**	54, **50**	7,920, **6,080**

EH = epoxide hydrolase; γ-GCS = gamma-glutamylcysteine synthesase; GST = glutathione S-transferase

[a]Non-bold values for mouse; bold values for rat; values in italics were estimated by formal optimization; entries in italics indicate optimized parameter values; V_{max} values in nmol/hour/mg of protein; K_m values and tissue cysteine concentrations in mM.

Source: Kohn and Melnick 2001

Validation of the Model. The model predicted similar profiles of 1,3-butadiene and 3,4-epoxy-1-butene uptake data (100–4,000 ppm) in mice and rats against which it was optimized. Further, it predicted single time point concentrations of 1,3-butadiene in mice and rats similar to observations from nose-only exposures to 7–1,250 ppm (Bond et al. 1986; Himmelstein et al. 1994). Additionally, it predicted similar percentages of GSH depletion in mouse and rat lung and liver observed following 7-hour 1,3-butadiene exposures of 50–2,000 ppm (Deutschmann and Laib 1989).

Target Tissues. The model simulates concentrations of 1,3-butadiene and 3,4-epoxy-1-butene in lung, liver, and kidney, all target tissues for 1,3-butadiene metabolite intoxication, as well as in blood, fat, gastrointestinal tract, and lumped compartments for muscle and viscera.

Species Extrapolation. The model has been developed for simulations of rats and mice. Extrapolation of predictions to humans would require additional species-specific values for physiology and metabolism, as well as human data to verify the accuracy of the predictions.

High-low Dose Extrapolation. The model has been evaluated for simulating inhalation exposures ranging from 7 to 4,000 ppm.

Interroute Extrapolation. The model simulates inhalation exposures only and would require additional parameterization to simulate exposures by other routes.

Strengths and Limitations. Strengths of the model are that it simulates disposition and clearance of inhaled 1,3-butadiene, as well as production and clearance of the major oxidative metabolites of 1,3-butadiene in kidney, liver, and lung, including 3,4-epoxy-1-butene, 1,2:3,4-diepoxybutane, 3,4-epoxy-1,2-diol, and 3-butene-1,2-diol. It also simulates production and utilization of GSH in the kidney, lung, and liver, which allows prediction of glutathione depletion resulting from 1,3-butadiene metabolism. Limitations include: (1) the model has not been evaluated against data for inhalation exposures in humans, and (2) the model does not simulate the appearance and disposition of other metabolites, such as the diepoxide, diols, and GSH-conjugate products eliminated in the urine.

Brochot et al. 2007

Description of the Model. The Brochot model (Brochot and Bois 2005; Brochot et al. 2007) simulates absorption of 1,3-butadiene and the disposition of 1,3-butadiene, 1,2-epoxy-3-butene, and 1,2:2,3-diepoxybutane in the blood, fat, and lumped compartments for richly- and poorly-perfused tissues in humans. Model parameters are presented in Table 3-8. In addition, the disposition and clearance of 3-butene-1,2-diol and 3,4-epoxy-1,2-butanediol was modeled for the blood and richly- and poorly-perfused tissues. Tissue:blood partition coefficients were taken from the literature. 1,3-Butadiene is eliminated by exhalation to lung air or oxidative metabolism, epoxide hydrolysis, or GSH conjugation in the richly-perfused tissues to mono- and diepoxide and the two diols. Since the model was intended to direct further study design for low-ppm human exposures, all of the metabolic steps are described as 1^{st}-order processes, governed by a rate constant for each pathway. The metabolic rate constants and physiological parameters were optimized using Bayesian techniques against 133 datasets from individual subjects inhaling 2 ppm 1,3-butadiene for 20 minutes (Lin et al. 2001). Several extensions of the Brochot et al. (2007) model have been reported. A 23-compartment model was developed for simulating 1,3-butadiene and 1,2-epoxy-3-butene kinetics in humans (Péry and Bois 2009). The model simulates flow-limited distribution to each tissue with partitioning assumed to occur predominantly into tissue fat (estimated from the fat:blood partition coefficient and fat content of each tissue). Beaudouin et al. (2010) further extended this model to a generic human lifetime PBPK model that included growth and transplacental transfer to the fetus.

Risk Assessment. This model has not been used in risk assessment.

Validation of the Model. The model fit well against the human data from which it was calibrated. Its performance has not been evaluated against other independent human inhalation data.

Target Tissues. The model predicts parent compound, mono- and diepoxide, and viscinal thiol (including the epoxydiol) concentrations in the blood, but not in other tissues.

Species Extrapolation. The model was optimized for humans. Extrapolation of predictions to animals would require additional species-specific values for physiology and metabolism, as well as animal data (available in the literature) to verify the accuracy of the predictions.

Table 3-8. Physiological and Chemical Parameters Used in the Brochot et al. 2007 PBPK Model for 1,3-Butadiene Humans

Parameter	Mean[a]	Standard deviation[a]
Body weight (kg)	70	
Sex	M	
Metabolic activity in liver (mg protein/kg liver)		
Microsomal protein	14,500	
Cytosolic protein	45,000	
Relative weight (percent of body weight)		
Liver	0.026	
Relative volumes (percent of body weight)		
Well-perfused tissues	0.10	0.02
Fat	0.21	0.05
Relative flows (percent of total blood flow)		
Poorly perfused tissues	0.26	0.06
Fat	0.05	0.01
Pulmonary characteristics		
Minute volume (L/minute)	7.5	1.87
Ventilation perfusion ratio	1.0	0.25
Dead space fraction	0.33	0.08
Partition coefficients for BD		
Blood:air	1.22	0.30
Poorly perfused tissues:blood	0.72	0.18
Well-perfused tissues:blood	0.69	0.17
Fat:blood	18.4	4.6
Partition coefficients for EB		
Blood:air	93.3	23.3
Poorly perfused tissues:blood	0.49	0.12
Well-perfused tissues:blood	0.59	0.15
Fat:blood	1.80	0.45
Partition coefficients for DEB		
Poorly perfused tissues:blood	1.98	0.49
Well-perfused tissues:blood	1.53	0.38
Fat:blood	2.20	0.55
Partition coefficients for BDD		
Poorly perfused tissues:blood	1.00	0.25
Well-perfused tissues:blood	1.00	0.25
Partition coefficients for EBD		
Poorly perfused tissues:blood	1.00	0.25
Well-perfused tissues:blood	1.00	0.25
Metabolic constants ($minute^{-1}$)		
BD → EB	0.119	0.06

Table 3-8. Physiological and Chemical Parameters Used in the Brochot et al. 2007 PBPK Model for 1,3-Butadiene Humans

Parameter	Mean[a]	Standard deviation[a]
Metabolic constants		
EB → DEB	0.020	0.01
EB → BDD	0.511	0.25
DEB → EBD	0.471	0.23
BDD → EBD	0.008	0.01
Other transformations (L/kg liver/minute)		
EB by GSH	0.195	0.10
DEB by GSH	0.113	0.06
EBD by GSH	0.056	0.03
EBD by hydrolysis	0.235	0.12
BDD by ADH	0.045	0.02

[a]Mean and standard deviation of lognormal distributions, reflecting variability in the human population.

ADH = alcohol dehydrogenase; BD = 1,3-butadiene; BDD = 3-butene-1,2-diol; DEB = 1,2:3,4-diepoxybutane; EB = 1,2-epoxy-3-butene; EBD = 3,4-epoxy-1,2-butanediol; GSH = glutathione

Source: Brochot et al. 2007

High-low Dose Extrapolation. The model was calibrated for low (2 ppm) exposures in humans. Extrapolation to higher doses will require that the metabolic expression be modified to account for saturation of the oxidative, hydrolytic, and conjugating pathways described.

Interroute Extrapolation. The model was designed to simulate inhalation exposures. Additional parameters and absorption expressions must be added (and optimized with oral or dermal data) in order to extrapolate internal dosimetry from inhalation exposures across other routes of exposure. Parameters for gastrointestinal absorption of 1,3-butadiene were reported for use in a generic lifetime model (Beaudouin et al. 2010).

Strengths and Limitations. The model is the first PBTK model to simultaneously predict blood levels of 1,3-butadiene and its epoxide and viscinal diol metabolites in humans. Limitations include: (1) the model has not been evaluated against data for inhalation exposures in animals, and (2) the model does not account for saturation of metabolic pathways that may occur in humans (and have been observed in rodents) exposed to higher inhalation concentrations of 1,3-butadiene.

Sweeney et al. 2001

Description of the Model. The Sweeney et al. (1996, 1997, 2001) model simulates inhalation absorption of 1,3-butadiene and the disposition of 1,3-butadiene, 1,2-epoxy-3-butene, and 1,2:2,3 diepoxybutane in mice, rats, and humans. Blood, fat, liver, and lumped compartments for richly- and poorly-perfused tissues are simulated. Model parameters are presented in Table 3-9, 3-10, 3-11, 3-12, 3-13, 3-14, and 3-15. 1,3-Butadiene is eliminated by exhalation to lung air or oxidative metabolism to 1,3-epoxide-3-butene or to other products (e.g., aldehydes) in liver. The monoepoxide (1,3-epoxide-3-butene) undergoes further oxidative metabolism to the diepoxide (DEB) and both the mono- and diepoxide undergo epoxide hydrolysis, GSH conjugation, or nonenzymative degradation. Enzymatic reactions are simulated as saturable reactions (K_m, V_{max}) and non-enzymatic elimination reactions are simulated as first-order reactions. Production and utilization of glutathione in liver are simulated, which allows prediction of glutathione depletion resulting from 3,4-epoxy-1-butene metabolism.

Risk Assessment. This model has not been used in risk assessment.

Table 3-9. Physiological Parameters Used in Sweeney et al. (1997) 1,3-Butadiene PBPK Model

Parameter	Rat	Mouse
Alveolar ventilation[a] (Q_{pu}) (L/hour/kg)	17	41
Cardiac output[a] (Q_t) (L/hour/kg)	17	41
Body weight (BW) (kg)	0.215–0.475	0.028–0.035
Blood flow[b] (Q_i) (fraction of cardiac output) (F_i) (dimensionless)		
Lung	1.0	1.0
Fat	0.09	0.09
Slowly perfused tissues	0.15	0.15
Richly perfused tissues	0.51	0.51
Liver	0.25	0.25
Organ volumes[c] (V_i) (fraction of body weight) (dimensionless)		
Lung	0.0053	0.005
Fat	0.09	0.10
Slowly perfused tissues	0.71	0.7
Richly perfused tissues	0.0347	0.0226
Liver	0.05	0.0624

[a]Alveolar ventilation and cardiac output are given for a hypothetical 1-kg animal. In the model simulations, the parameter is multiplied by the body weight of the animal (in kg) to calculate the ventilation rate and cardiac output (in L/hour) for that individual animal.
[b]Tissue blood flows are calculated by multiplying the total cardiac output by the fractional flow: $Q_i = F_i \times Q_t$.
[c]Tissue volumes are calculated by multiplying the body weight by the fractional volume: $V_i = F_i \times BW$.

Source: Sweeney et al. 1997

Table 3-10. Partition Coefficients Used in Sweeney et al. (1997) PBPK Model for 1,3-Butadiene

	Butadiene[a]		Epoxybutene[a]		Diepoxybutane[b]
Tissue	Rat	Mouse	Rat	Mouse	Mouse
Blood	1.49	1.34	50.4	36.6	0.437
Liver	1.19	1.35	72.0	42.1	0.615
Lung	0.92	1.47	54.7	56.3	ND
Kidney	ND	ND	ND	ND	ND
Muscle	1.47	4.01	19.8	23.6	0.795
Fat	22.2	19.2	138.0	91.2	0.959
Saline	0.088		44.3		0.723
Oil	23.2		164		ND

[a]Tissue:air partition coefficients.
[b]Tissue:hexane partition coefficient.

ND = not determined

Source: Sweeney et al. 1997

Table 3-11. Nonenzymatic Reaction Rate Constants Used in Sweeney et al. (1997) PBPK Model for 1,3-Butadiene

	Epoxybutene		Diepoxybutane	
Tissue	Rat	Mouse	Rat	Mouse
Blood	0.582	0.558	ND	0.189
Liver	4.94	4.14	ND	3.15
Lung	6.07	2.70	ND	4.1
Fat	1.72	1.56	ND	2.8
Muscle	0	0	ND	0

ND = not determined

Source: Sweeney et al. 1997

Table 3-12. Metabolism Rate Constants Used in the Sweeney et al. (1997) PBPK Model for 1,3-Butadiene

				Parameter value	
Substrate	Tissue	Pathway	Units	Rat	Mouse
Butadiene	Liver	Oxidation	µmol/kg/hour	62	338
		(to all products)	µmol/L	3.75	2.0
		Oxidation	µmol/kg/hour	8.2	97
		(to epoxybutene only)	µmol/L	1.54	0.88
		Oxidation	µmol/kg/hour	54	243
		(to other volatiles)	µmol/L	4.36	2.72
	Lung	Oxidation	µmol/kg/hour	1.01	21.6
		(to all products)	µmol/L	7.75	5.01
		Oxidation	µmol/kg/hour	0.13	6.4
		(to epoxybutene only)	µmol/L	3.18	1.6
		Oxidation	µmol/kg/hour	0.88	16.1
		(to other volatiles)	µmol/L	9.14	9.5
Epoxybutene	Liver	Oxidation	µmol/kg/hour	57.1	176.6
		(one enzyme)	µmol/L	141	145
		Oxidation	µmol/kg/hour	10	32.5
		(two enzymes)	µmol/L	141	15.6
			µmol/kg/hour	47.1	144.1
			µmol/L	141	145
		Hydrolysis	µmol/kg/hour	260	754
			µmol/L	260	1,590
		Glutathione conjugation	µmol/kg/hour	78,100	154,000
			µmol/L	13,800	35,300
			µmol/L	100	100
	Lung	Glutathione conjugation	µmol/kg/hour	819	4,088
			µmol/L	17,400	36,500
Diepoxybutane	Liver	Hydrolysis	µmol/kg/hour	5,555	4,193
			µmol/L	2,700	8,100
		Glutathione conjugation	µmol/kg/hour	60,264	50,342
			µmol/L	24,000	6,400
	Lung	Hydrolysis	µmol/kg/hour	122.7	466.1
			µmol/L	7,100	7,500
		Glutathione conjugation	µmol/kg/hour	332	577
			µmol/L	4,170	1,700

Source: Sweeney et al. 1997

Table 3-13. Physiological Parameters Used in the Sweeney et al. (2010) PBPK Model for 1,3-Butadiene in Humans

Parameter	Value	Units	Comment
Alveolar ventilation rate (QPC)	4.3	L/hour/kg body weight	QP = QPC x BW
Cardiac output (QCC)	4.5	L/hour/kg body weight	QC = QCC x BW
Fractional blood flow to liver	0.227	Dimensionless	QR = 0.76 x QC−QL
Fractional blood flow to fat	0.052	Dimensionless	QS = 0.24 x QC−QF
Fractional weight of liver	0.027	Dimensionless	
Fractional weight of lung	0.0076	Dimensionless	VR = 0.09−VL−VLU
Fractional weight of fat	0.2142	Dimensionless	VS = 0.81−VF
Body weight	70	kg	
Cytosolic protein content of liver	89,000	mg protein/kg liver	Rat value
Microsomal protein content of liver	77,000	mg protein/kg liver	Human value

Source: Sweeney et al. 2001

Table 3-14. Chemical Partition Coefficients Used in the Sweeney et al. (2010) PBPK Model for 1,3-Butadiene in Humans

Parameter	Value	Comment
	1,3-Butadiene	
Blood:air	1.22	Average of individual values for humans
Liver:air	0.68	Human tissue
Fat:air	22.5	Human tissue
Lung:air	0.48	Human tissue
Slowly perfused tissue:air	0.88	Value for human muscle
Richly perfused tissue:air	0.84	Values for human kidney, brain, and liver weighted by contribution to body weight
	Butadiene monoepoxide	
Blood:air	93.3	Human tissue
Liver:air	55.3	Human tissue
Fat:air	168	Human tissue
Lung:air	55.3	Value measured for human liver
Slowly perfused tissue:air	45.8	Value measured for human muscle
Richly perfused tissue:air	55.3	Value measured for human liver
	Butene diol	
Liver:blood	1	Volume of distribution=0.87 L/kg in mouse; mouse model has perfused tissues=0.9 kg/kg total body weight
Rest of body:blood	1	Volume of distribution=0.87 L/kg in mouse; mouse model has perfused tissues=0.9 kg/kg total body weight
	Butadiene diepoxide	
Liver:blood	1.53	Rat tissue
Fat:blood	2.2	Rat tissue
Lung:blood	1.53	Rat liver value
Slowly perfused tissue:air	1.82	Rat muscle value
Richly perfused tissue:air	1.41	Rat kidney value
	Epoxybutane diol	
Liver:blood	1	Assumption based on butene diol and butadiene diepoxide partition coefficients
Rest of body:blood	1	Assumption based on butene diol and butadiene diepoxide partition coefficients

Source: Sweeney et al. 2001

Table 3-15. Chemical Metabolism Parameters Used in the Sweeney et al. (2010) PBPK Model for 1,3-Butadiene in Humans

Parameter (units)	Baseline value[a]
V_{max} for epoxidation of 1,3-butadiene to butadiene monoepoxide (µmol/mg protein/hour)	0.0132
K_m for epoxidation of 1,3-butadiene to butadiene monoepoxide (µM)	0.7
V_{max} for epoxidation of butadiene monoepoxide to butadiene diepoxide (µmol/mg microsomal protein/hour)	0.031
K_m for epoxidation of butadiene monoepoxide to butadiene diepoxide (µM)	880
V_{max} for hydrolysis of butadiene monoepoxide to butene diol	1.4
K_m for hydrolysis of butadiene monoepoxide to butene diol	540
V_{max} for conjugation of butadiene monoepoxide and glutathione (µmol/mg cytosolic protein/hour)	2.7
K_m for conjugation of butadiene monoepoxide and glutathione (µM)	10,400
V_{max} for conjugation of butadiene diepoxide and glutathione (µmol/mg cytosolic protein/hour)	0.4
K_m for conjugation of butadiene diepoxide and glutathione (µM)	3,390
V_{max} for epoxidation of butene diol to epoxybutane diol (µmol/mg microsomal protein/hour)	0.031
K_m for epoxidation of butene diol to epoxybutane diol (µM)	880
V_{max} for hydrolysis of butadiene diepoxide to epoxybutane diol (µmol/mg microsomal protein/hour)	9.2
K_m for hydrolysis of butadiene diepoxide to epoxybutane diol (µM)	4,605
V_{max} for metabolism of butene diol by alcohol dehydrogenase (µmol/mg cytosolic protein/hour)	0.64
K_m for metabolism of butene diol by alcohol dehydrogenase (µM)	10,600
V_{max} for hydrolysis of epoxybutane diol to erythritol (µmol/mg microsomal protein/hour)	4.6
K_m for hydrolysis of epoxybutane diol to erythritol (µM)	4,605
V_{max} for conjugation of epoxybutane diol and glutathione (µmol/mg cytosolic protein/hour)	0.2
K_m for conjugation of epoxybutane diol and glutathione (µM)	3,390

[a]Median or average parameter values.

Source: Sweeney et al. 2001

Validation of the Model. The model was calibrated and evaluated against data from intravenous studies in rats and inhalation exposures of mice and rats (Sweeney et al. 1997) and humans (Sweeney et al. 2001).

Target Tissues. The model has been used to predict parent compound, monoepoxide, and diepoxide concentrations in the blood.

Species Extrapolation. Mouse, rat, and human models have been developed. Extrapolation of predictions to animals would require additional species-specific values for physiology and metabolism, as well as animal data (available in the literature) to verify the accuracy of the predictions.

High-low Dose Extrapolation. The model has been evaluated for simulating inhalation exposures in mice and rats ranging from 60 to 1,250 ppm in rodents and 5 ppm in humans.

Interroute Extrapolation. The model was designed to simulate inhalation exposures. Additional parameters and absorption expressions must be added (and optimized with oral or dermal data) in order to extrapolate internal dosimetry from inhalation exposures across other routes of exposure.

Strengths and Limitations. Strengths of this model include simulation of an alternative oxidative pathway for 1,3-butadiene (other than leading to 1,2-epoxy-3-butene); simulations of both enzymatic and nonenzymatic elimination of 1,3-butadiene metabolites; and simulation of production and utilization of glutathione.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Formation of Reactive Metabolites. The role of metabolism of 1,3-butadiene to reactive metabolites and the importance of species differences in metabolism of 1,3-butadiene to human health risk assessment were recently reviewed by Kirmam et al. (2010a). As discussed in Section 3.4.3 (Toxicokinetics/ Metabolism; also see Figure 3-2), 1,3-butadiene is metabolized by oxidation, hydrolysis, and conjugation reactions, with oxidation and hydrolysis reactions leading to the formation of several reactive epoxide intermediates. Of the reactive intermediates formed, EB (formed by oxidation of 1,3-butadiene), DEB (formed by oxidation of EB), and EBD (formed by hydrolysis reactions of DEB) are reactive electrophilic

compounds that have been shown to interact with DNA. The order of genotoxic potency of the epoxide metabolites is DEB >> EB > EBD. The higher genotoxic potency of DEB may be due to its ability to bind to two molecules or two places in the molecule at the same time (e.g., DNA-protein cross-links or DNA cross-links) (see discussion below in Section 3.5.2 on mechanisms of genotoxicity) (Albertini et al. 2010). Thus, the formation of reactive metabolites is critical to the genotoxic activity of 1,3-butadiene. Although little information was identified regarding the role of reactive metabolites in the development of other adverse effects of 1,3-butadiene (e.g., nongenotoxic, noncancer), given their reactive nature, it is likely that reactive epoxide metabolites play an important role in the development of other adverse effects.

Species Differences in Metabolism. Metabolism of 1,3-butadiene appears to follow the same enzymatic pathways in all species, including humans, with production of the same reactive intermediates. However, as discussed below, important species differences exist in the rates of formation and detoxification of reactive metabolites (Bond et al. 1993; Csanády et al. 1992; Dahl et al. 1991; Filser et al. 2001, 2007, 2010; Himmelstein et al. 1997; Henderson et al. 1996, 2001; Kirman et al. 2010a; Krause and Elfarra 1997; Schmidt and Loeser 1985; Thornton-Manning et al. 1995a). As a result, rodents, particularly mice, have much higher tissue levels of reactive metabolites than nonhuman primates and humans. Therefore, based on the assumption that the same mechanism of action is involved in the development of 1,3-butadiene-induced toxicity (i.e., interaction of the reactive metabolites with DNA and other cellular macromolecules) is the same for all species, mice are expected to be much more sensitive to 1,3-butadiene than other rats, nonhuman primates, and humans.

As reviewed by Kirman et al. (2010a), evidence for species differences in metabolism of 1,3-butadiene is available from *in vitro* studies, studies using isolated perfused livers, and *in vivo* studies measuring tissue and urine metabolite levels and blood hemoglobin adduct levels. Results of *in vitro* studies using hepatic microsomal fractions isolated from mice, rats, and humans show that conversion of EB to DEB in mice is 3.3-fold greater than in rats and 2.4–61-fold greater than in humans. Studies in isolated perfused livers show differences in metabolism of 1,3-butadiene in mice and rats. In livers perfused with 1,3-butadiene, three epoxide metabolites (EB, DEB, and EBD) were identified in perfusion effluent in mice, whereas only one epoxide metabolite (EB) was identified in rats. Effluent concentrations of EB in mice were 8.5-fold greater than in rats. For perfusion studies with EB (which is oxidized to form DEB), DEB formation was greater in mice than in rats. Metabolite levels in tissues following inhalation exposure of mice and rats to 1,3-butadiene also provide evidence of species differences. Compared to rats, EB and DEB levels in blood and tissues of mice were from approximately 2–15- and >100-fold higher,

respectively, with levels exhibiting dose- and time-dependence (see discussion below on nonlinear kinetics) (Filser et al. 2007). Based on evaluation of hemoglobin adduct biomarkers (adducts formed by interaction of 1,3-butadiene metabolites with hemoglobin), mice appear to have higher DEB levels than rats and much higher levels than humans (Swenberg et al. 2011). However, quantitative measurements of differences in hemoglobin adduct profiles show considerable variability, possibly due to differences in exposure conditions. Comparison of urinary excretion profiles of 1,3-butadiene metabolites in mice, rats, and humans also shows that species differences exist in the detoxification pathways. Findings suggest that humans and rats are more "efficient" at detoxification of reactive metabolites than mice. Taken together, results of *in vitro* and *in vivo* studies showing that mice have higher levels of reactive metabolites, particularly the highly reactive DEB, than other species suggest that mice may be uniquely sensitive to toxic effects of 1,3-butadiene and, therefore, may not be an appropriate animal model for use in human health risk assessment of 1,3-butadiene.

Nonlinear Toxicokinetics (Metabolism). Metabolism of 1,3-butadiene exhibits nonlinear kinetics (Kirman et al. 2010a), with both dose- and duration-dependent effects (see discussion in Section 3.4.3 Toxicokinetics/Metabolism). Because the formation of reactive metabolites are critical in the development of 1,3-butadiene toxicity, nonlinearity in metabolic processes has the potential to affect dose-response extrapolation from animals to humans. Several processes have been proposed as sources of nonlinear kinetics; these include inhibition, induction and saturation of various metabolizing enzymes and depletion of glutathione (as reviewed by Kirman et al. 2010a).

3.5.2 Mechanisms of Toxicity

Genotoxicity. The genotoxicity of 1,3-butadiene and its electrophilic metabolites have been extensively studied. A comprehensive review of the genotoxicity of 1,3-butadiene metabolites, focusing primarily on EB, DEB, and EDB, was recently published (Albertini et al. 2010). The weight of evidence strongly suggests that 1,3-butadiene metabolites, rather than 1,3-butadiene itself, are responsible for genotoxic effects, due to their highly reactive nature. Of these metabolites, the order of potency for mutagenicity is DEB >> EB > EDB. Results of *in vitro* studies in bacterial and mammalian cells (including human cells) show that the electrophilic metabolites of 1,3-butadiene form DNA adducts, induce DNA strand breaks, increase unscheduled DNA synthesis and DNA excision repair, induce sister-chromatid exchange, induce micronucleus formation, and produce mutations, chromosome aberrations (including breaks), and aneuploidy (as reviewed by Albertini et al. 2010). Results of *in vivo* studies in animals show that 1,3-butadiene metabolites form adducts with DNA (Koturbash et al. 2011a, 2011b). Other studies evaluating genotoxicity following inhalation exposure to 1,3-butadiene provide indirect evidence of

genotoxicity of 1,3-butadiene metabolites (Cunninham et al. 1986; Jauhar et al. 1988; Lovreglio et al. 2006; Sharief et al. 1986; Sram e tal. 1998; Tice et al. 1987).

Carcinogenicity. As discussed in Section 3.2.1.7, chronic exposure to 1,3-butadiene is associated with an increased risk of mortality due to leukemia in styrene-butadiene workers and the development of multisite cancers in laboratory rodents. The mode of action for carcinogenicity of 1,3-butadiene was recently assessed by Kirman et al. (2010b). As discussed above (Mechanism of Toxicity, Genotoxicity), the genotoxicity of electrophilic metabolites of 1,3-butadiene (DEB, EB, and EBD) have been extensively studied. Results show that DEB, EB, and EBD react with DNA and are mutagenic. Based on the weight of evidence for genotoxicity, it is likely that the carcinogenic mode of action of 1,3-butadiene is mutagenic activity of the electrophilic 1,3-butadiene metabolites.

Ovarian atrophy. Intraperitoneal studies in mice suggest that 1,3-butadiene metabolites are the causative agent for the ovarian effects observed in intermediate- and chronic-duration inhalation studies (NTP 1993). Dose-related decreases in ovarian and uterine weights, number of small (primordial) ovarian follicles, and number of growing (primary to pre-antral) ovarian follicles were observed following a 30-day intraperitoneal exposure to EB or DEB (Doerr et al. 1996). The ED_{50} (i.e., the effective dose that reduces the number of follicles to 50% of controls) values for small and growing follicles were 0.29 and 0.40 mmol/kg, respectively, for EB and 0.10 and 0.14 mmol/kg, respectively, for DEB. Similarly, decreases in ovarian or uterine weight and the number of ovarian follicles were also observed in rats similarly exposed to DEB (Doerr et al. 1996). However, no alterations were observed in rats administered EB at doses as high as 1.43 mmol/kg. These data strongly suggest that DEB is the causative agent of the ovarian atrophy.

Although similar effects were observed in rats and mice administered DEB, mice appear to be more sensitive to its toxicity than rats. Administration of 0.14 mmol/kg resulted in 83 and 52% depletion of small and growing follicles, respectively, in mice and only 31 and 40% reductions in rats. When the dose-response plot for ovarian weight is based on area under the blood EB or DEB concentration-time curve (estimated using PBPK modeling), the curves are similar for both species (Sweeney et al. 2001). Sweeney et al. (2001) also used PBPK modeling to estimate the blood area under the DEB concentration-response curve using the data from the NTP (1993) study, which found ovarian effects in mice exposed to ≥6.25 ppm, and from the Owen study (Owen and Glaister 1990; Owen et al. 1987), which did not find ovarian effects in rats exposed to ≤8,000 ppm. In mice, the blood area under the DEB curve was consistent with the results of the Doerr et al. 1996) intraperitoneal study. The blood DEB area under the

curve for rats exposed to 8,000 ppm 6 hours/day, 5 days/week for 105 weeks would be 189 μM-hour; this value lies between the predicted NOAEL and LOAEL for ovarian effects in rats administered DEB via intraperitoneal injection.

3.5.3 Animal-to-Human Extrapolations

Comparison of rat and mouse data identify large differences in sensitivity to 1,3-butadiene, which are due to metabolic differences between species. Humans, rats, and mice metabolize 1,3-butadiene using the same enzymatic pathways resulting in the production of the same reactive metabolites, in particular, EB, DEB, and EBD. However, quantitative differences in the rate of formation and detoxification of reactive metabolites have been found that result in higher tissue levels of reactive metabolites in rodents, particularly mice, than in humans (Bond et al. 1993; Csanády et al. 1992; Dahl et al. 1991; Filser et al. 2001, 2007, 2010; Henderson et al. 1996, 2001; Himmelstein et al. 1997; Kirman et al. 2010a; Krause and Elfarra 1997; Schmidt and Loeser 1985; Thornton-Manning et al. 1995b). *In vitro* and perfusion data show that mice are more efficient than rats at oxidizing 1,3-butadiene to form EB, and the conversion of EB to DEB in mice is 3.3-fold greater than in rats and 2.4–61-fold greater than in humans (Kirman et al. 2010a). In addition, mice have a higher ratio of 1,3-butadiene activation to detoxification than rats or humans; the ratio of activation to detoxification was 74:1 in mouse, 6:1 in rat, and 6:1 in human liver tissues (Bond et al. 1993).

Following inhalation exposure to 1,3-butadiene, blood and tissue levels of EB and DEB were 2–15- and >100-fold higher, respectively, in mice as compared to rats (Filser et al. 2007). At equivalent inhalation concentrations, the total amount of 1,3-butadiene metabolites were 5–50 times lower in cynomolgus monkeys than in mice and 4–14 times lower in monkeys compared to rats (Dahl et al. 1991). Swenberg et al. (2011) estimated DEB blood levels measured 1,3-butadiene-derived hemoglobin adducts levels in rats, mice, and humans exposed to approximately 1 ppm 1,3-butadiene. The estimated DEB doses were 0.02, 0.42, and 24 nM-hour/ppm-hour in humans, rats, and mice, respectively. Thus, the extrapolation of rodent data to humans would require the use of an internal dose metric to account for these species differences in the metabolism of 1,3-butadiene. Although PBPK models have been developed in rodents (Johanson and Filser 1993; Kohn and Melnick 1993, 1996, 2000) and a preliminary model has been developed in humans (Brochot et al. 2007), the models are limited in their ability to predict internal doses for key metabolites (Kirman and Grant 2012). An alternative approach to using PBPK models would be to use a biomarker of exposure to the reactive metabolites. Several biomarkers of exposure have been identified for reactive 1,3-butadiene metabolites including MHB-Val hemoglobin adducts, *N*-(2,3,4-tri-

hydroxybutyl)valine (THB-Val) hemoglobin adducts, and *pyr*-Val hemoglobin adducts, which have been shown to be good surrogate biomarkers for EB, EBD, and DEB, respectively (Georgieva et al. 2010; Slikker et al. 2004).

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No *in vivo* or *in vitro* studies were located regarding endocrine disruption in humans and/or animals after exposure to 1,3-butadiene.

3.7 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

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

child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No human data are available to determine whether children are more sensitive than adults to 1,3-butadiene toxicity. Mechanistic data in animals suggest that the ratio of 1,3-butadiene oxidation:epoxide hydrolysis may be a significant determinant of 1,3-butadiene sensitivity (see Sections 3.5.1 and 3.5.2). It is not known if the ratio of 1,3-butadiene oxidation:epoxide hydrolysis is different in children than adults. Unborn children may be more sensitive to 1,3-butadiene toxicity than adults, as changes in fetal body weight and developmental effects have been identified at the lowest LOAELs in mice exposed to acute- and intermediate-duration inhalation exposures (Anderson et al. 1996; DOE/NTP 1987b). Several studies have associated the development of childhood leukemia to close proximity of birthplace to industrial point sources of 1,3-butadiene (and other high-volume industrial chemicals, including benzene) (Knox et al. 2005, 2006; Reynolds et al. 2003; Whitworth et al. 2008). Although these study authors suggest that *in utero* exposure to 1,3-butadiene may have significantly contributed to cancer risks in these populations, there are no estimates of actual prenatal or postnatal exposures of mothers or children, respectively.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,3-butadiene are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,3-butadiene are discussed in Section 3.8.2.

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,3-Butadiene

Two urinary metabolites of 1,3-butadiene have been identified in tollbooth workers. Sapkota et al. (2006) measured 258–378 ng/mL 1,2-dihydroxy-4-(N-acetylcysteinyl)-butane and 6–9.7 ng/mL of the isomeric mixture of 1-hydroxy-2-(N-acetylcysteinyl)-3-butene and 1-(N-acetylcysteinyl)-2-hydroxy-3-butene in

workers' urine following average ambient 1,3-butadiene exposures of 0.4–1 ppb. These biomarkers are quite specific to 1,3-butadiene exposure, but the measured levels were not significantly associated with exposure, although this may have been due to the small sample size used or the low (0.0005 ppm) exposure levels studied. N-acetyl-S-((1-hydroxymethyl)-2-propenyl)cysteine and N-acetyl-S-((2-hydroxymethyl)-3-propenyl)cysteine, the isomeric mixture known as MHBMA (or M2), are the GST conjugation products of EB found in human urine following 1,3-butadiene exposure. Another urinary metabolite, N-acetyl-S-(3,4-dihydroxybutyl)cysteine, or DHBMA (M1), is formed by EBdiol conjugation with glutathione via GST (Boogaard et al. 2001a; McDonald et al. 2004). These urinary metabolites have been used as biomarkers of 1,3-butadiene exposures in several human studies (Albertini et al. 2001, 2007; Ammenheuser et al. 2001; Boogaard et al. 2001a; Fustinoni et al. 2004).

Protein adducts have been widely used to monitor the formation of alkylating metabolites and can be used as dose metrics to compare species differences in metabolism. Hemoglobin adducts accumulate over the lifespan of the erythrocyte and they represent cumulative exposure since they are not removed by enzymatic repair systems (Georgieva et al. 2010). Three N-terminal valine hemoglobin adducts have been identified for 1,3-butadiene: MHB-Val, THB-Val, and *pyr*-Val. MHB-Val, THB-Val, and *pyr*-Val are formed when EB, DEB, and EB-diol, respectively, react with hemoglobin (Georgieva et al. 2010; Slikker et al. 2004). A linear accumulation of MHB-Val and THB-Val was observed in B6C3F1 mice and Sprague-Dawley rats after intraperitoneal (Sun et al. 1989b) and inhalation (HEI 2000) exposures. Species differences have been detected in the amount of adducts formed at a given 1,3-butadiene concentration. Higher levels of MHB-Val and *pyr*-Val adducts were found in mice compared to rats (Albrecht et al. 1993; Boysen et al. 2004). Concentration-response studies have shown that the formation of *pyr*-Val hemoglobin adducts is saturable. In rats, the formation of *pyr*-Val adducts plateaus at inhalation exposures of ≥200 ppm (Georgieva et al. 2010). In mice, the formation of *pyr*-Val adducts did not plateau; however, the rate of formation decreased below 1.5 ppm (Georgieva et al. 2010). MHB-Val and THB-Val hemoglobin adduct levels were well correlated with 1,3-butadiene exposure in 1,3-butadiene monomer workers (Albertini et al. 2001, 2007; Begemann et al. 2001a, 2001b; Osterman-Golkar et al. 1996) and Chinese polymer workers (Hayes et al. 2000; HEI 2000). *Pyr*-Val was not detected in blood of male and female Czech workers exposed to 0.2–0.4 ppm (Albertini et al. 2007). *Pyr*-Val adducts were detected in the blood of workers not occupationally exposed to 1,3-butadiene, in monomer workers and polymerization workers (Boysen et al. 2012); the levels in the polymerization workers (mean 1,3-butadiene exposure level of 0.81 ppm) were significantly higher than in the control and monomer workers (mean 1,3-butadene exposure levels of 0.01 and 0. 29 ppm, respectively). When the three groups of workers were combined, a significant association between *pyr*-Val adduct levels and

individual 1,3-butadiene exposure levels was found. Using levels of these hemoglobin adducts, Swenberg et al. (2011) estimated metabolite levels in rats, mice, and humans, which allowed for a species comparison of reactive metabolite levels at a given 1,3-butadiene concentration.

Zhao et al. (2000) found a significant linear relationship of DNA adduction and 1,3-butadiene exposure between 1,3-butadiene workers and controls. The levels of N1-(2,3,4-trihydroxybutyl)adenine adduct in lymphocytes of 1,3-butadiene workers (mean exposure: 0.3 ppm; range: <0.005–7.7 ppm) were 5-fold higher than controls (mean exposure: 0.01 ppm; range: <0.001–0.07 ppm). 1,3-Butadiene-specific urinary metabolites and hemoglobin and DNA adducts have also been observed in animals. Excretion of 1,3-butadiene metabolites was reported to be high in the urine of exposed monkeys (Dahl et al. 1990). DNA adducts were detected in the livers of mice and rats exposed to radiolabeled 1,3-butadiene (Kreiling et al. 1986b). In mice exposed to 1,3-butadiene by nose-only inhalation, the N7-guanine adduct (*N*7-(1-(hydroxymethyl)-2,3-dihydroxypropyl)guanine) from interaction with 3,4-epoxy-1,2-diol, was the major DNA adduct measured (Boogaard et al. 2001b).

1,3-Butadiene has been measured in expired air of forestry workers living in mountain villages (Perbellini et al. 2003); however, the levels measured (median of 1.2 ng/L) were not correlated with any exposure to 1,3-butadiene.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,3-Butadiene

Dermal, ocular, and/or upper respiratory irritation can occur following 1,3-butadiene exposure (NIOSH 2005) and may alert the exposed individual. However, the effects are not specific for 1,3-butadiene exposure and may be caused by several other chemicals.

Given the genotoxic (Section 3.3) and carcinogenic (Section 3.2.1.7) activity of 1,3-butadiene, a useful biomarker of effect would correlate a quantifiable measure of genetic mutation with 1,3-butadiene exposure. 1,4-Bis-(guan-7-yl)-2,3-butanediol (bis-N7G-BD) and 1-(guan-7-yl)-4-(aden-1-yl)-2,3-butanediol (N7G-N1A-BD) are DEB-specific DNA-DNA cross-links identified in rats and mice inhaling up to 625 ppm 1,3-butadiene (Goggin et al. 2009, 2011). Mice exhibited 4–10-fold higher levels than rats of these cross-links. Further, higher levels of bis-N7G-BD were measured in females, compared to males. The sensitivity of female mice to these biomarkers and to 1,3-butadiene-induced carcinogenicity suggests that: (1) DEB is the putative carcinogenic metabolite of 1,3-butadiene, and

(2) bis-N7G-BD and N7G-N1A-BD levels may quantitatively inform on genotoxicity leading to tumor development.

Another biomarker of genetic change is the mutation frequency of the *hprt* gene locus in human peripheral lymphocytes, which has been used in multiple studies of 1,3-butadiene SBR, monomer, and polymer workers in the United States, China, and Czech Republic. These studies are discussed in detail in Section 3.3. Several of these studies demonstrated good correlation between the increase in *hprt* mutation frequency and 1,3-butadiene exposure (Abdel-Rahman et al. 2001, 2003, 2005; Ammenheuser et al. 2001; Ma et al. 2000; Ward et al. 1994, 1996, 2001), as well as correlation with urinary and hematological biomarkers of exposure. Others did not find a significant correlation between exposure and mutation frequency (Albertini et al. 2001, 2007; Hayes et al. 1996, 2000; HEI 2003; Liu et al. 2008; Tates et al. 1996). The reasons for the differences in sensitivity of the *hprt* mutation as a biomarker may include the very low exposures that were studied and differences in assay procedures (as discussed in Section 3.3). It is unclear at this time which *hprt* mutation frequency assay is most adequate for risk assessment.

Two biomarkers for carcinogenic effect have been consistently found in multiple tumors sites in rodent chronic bioassays. A number of malignant gliomas and neuroblastomas in mice chronically inhaling 1,3-butadiene exhibited mutations of the p53 gene and H- and K-*ras* oncogenes (Kim et al. 2005), which have also been observed in forestomach tumors (Sills et al. 2001), hemagiosarcomas (Hong et al. 2000), and lymphomas (Zhuang et al. 1997) of chronically exposed mice.

3.9 INTERACTIONS WITH OTHER CHEMICALS

In addition to 1,3-butadiene, workers in the rubber industry are exposed to other chemicals, including styrene and its mutagenic metabolite, styrene oxide (Loprieno et al. 1978; Norppa et al. 1980; Pohlova et al. 1985; Watabe et al. 1978), as well as dithiocarbamates (Irons and Pyatt 1998). It is unclear whether these other chemicals or their active metabolites have a synergistic harmful effect in humans, but a multivariate analysis of an SBR worker cohort (HEI 2006) did not detect interactive effects of co-exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate (DMDTC). Animal studies have found that DMDTC can qualitatively and quantitatively effect the metabolism of 1,3-butadiene. *In vitro* studies show that DMDTC treatment decreases the metabolism of 1,3-butadiene to EB and the metabolism of epoxybutene to DEB in rats and mice (Green et al. 2001). Styrene has been shown to inhibit the metabolism of 1,3-butadiene in rats simultaneously exposed to both compounds (Laib et al. 1992;

Leavens et al. 1996). The inhibition was only observed at 1,000 ppm 1,3-butadiene concentration and not at 100 ppm (Leavens et al. 1996). However, blood levels of EB increased and the blood levels of DEB were unaffected by styrene co-exposure, as compared to exposure to 1,3-butadiene only (Leavens et al. 1996). Thus, co-exposure to styrene may not affect the toxicity of 1,3-butadiene. Inhalation exposure to 1,3-butadiene and styrene did not affect the genotoxic potential of 1,3-butadiene in mice (Leavens et al. 1997).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,3-butadiene than will most persons exposed to the same level of 1,3-butadiene in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 1,3-butadiene, or compromised function of organs affected by 1,3-butadiene. Populations who are at greater risk due to their unusually high exposure to 1,3-butadiene are discussed in Section 6.7, Populations with Potentially High Exposures.

The human and animal data do not identify a gender-specific susceptibility to 1,3-butadiene. Human *in vivo* data do not identify specific populations that may be sensitive to the effects of 1,3-butadiene. Polymorphisms in metabolic enzymes may affect the toxicokinetics of 1,3-butadiene and render some individuals more sensitive to toxicity, based on increased sensitivity to genetic changes seen in these groups. Lymphocytes from GSTT1-null 1,3-butadiene workers in Texas had higher induction of sister chromatid exchange following *in vitro* DEB exposure (Kelsey et al. 1995), while GSTT1-null Czech workers exhibited higher rates of chromosomal aberrations (Sorsa et al. 1996). However, no such effects were observed in other Czech (Sram et al. 1998) or Chinese (Hayes et al. 2000) workers that were GSTT1 or GSTM1 deficient. Increased *hprt* mutation frequencies have been reported in U.S. 1,3-butadiene workers with various polymorphisms in EH (Abdel-Rahman et al. 2001, 2003, 2005). In *in vitro* studies with human lymphocytes, EB induced higher levels of sister chromatid exchanges in GSTM1-null samples, as compared to GSTM1 samples (Uusküla et al. 1995), suggesting that the clastogenic change may the result of less EB being detoxified via GSTM1-mediated glutathione conjugation. Similarly, EB induced higher levels of sister chromatid exchanges in lymphocytes from GSTT1-null individuals, as compared to GSTT1-positive individual (Bernardini et al. 1998).

The relationship between polymorphisms and the urinary excretion of M1 and M2 metabolites has been exposed in studies of Czech 1,3-butadiene workers. GST polymorphisms resulted in shifts in the mean

ratio of M2/(M1 + M2) (indicative of the activity of EB glutathione conjunction pathway), which was significantly lower in GSTM1-null workers, as compared to GSTM1-positive workers (HEI 2003); a lower ratio was also found in the GSTT1-null workers, but it was not significantly different from the GSTT1-positive workers. No significant alterations in M1 or M2 concentrations or the ratio were found for workers genotyped for CYP2E1, EH, and ADH polymorphisms. Regression analysis revealed that the slopes of the 1,3-butadiene concentration-M2 levels and concentration-M2/(M1+M2) was significantly different in CYO2E1 D/D intron 6 polymorphism compared to workers who were heterozygous for C/D (HEI 2003). In a subsequent study by this group, a significant difference in M2/(M1+M2) ratio was observed in the GSTT1-null workers (Albertini et al. 2007). When different EH genotypes were combined into high, intermediate, and low activity phenotypes, significantly higher M2 levels were observed in the low activity genotype group (Albertini et al. 2007).

Animals studies indicate that the predominant factor in species sensitivity is related to the toxicokinetics of 1,3-butadiene, specifically, the ratio of P450-mediated oxidation:epoxide hydrolase activity (see Section 3.4.3). Human populations that have a higher ratio of 1,3-butadiene oxidation:hydrolysis metabolism may also be more sensitive, although such populations have not been identified. In terms of absorption capacity, Asian volunteers had about 20% greater fractional absorption of inhaled 1,3-butadiene than did Caucasians, African-Americans, or Hispanics (Lin et al. 2001). However, it is not known if this results in higher internal doses of the putative epoxide toxicants.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,3-butadiene. 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 1,3-butadiene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

3.11.1 Reducing Peak Absorption Following Exposure

No specific antidotes for 1,3-butadiene are available; however, recommendations have been made for general treatment of intoxicated persons (Bronstein and Currance 1988; Stutz and Janusz 1988). First, the exposed individual should be removed from the contaminated area and contaminated clothing should be taken away (Currance et al. 2007; Leikin and Paloucek 2002). It has been suggested that exposed skin should be washed with soapy water and contaminated eyes should be flushed with water. Inhalation

exposure to high 1,3-butadiene concentrations may result in narcosis leading to respiratory paralysis and death. Data have shown that neurological effects, including anesthesia have been observed in animals exposed to 250,000 ppm (Carpenter et al. 1944). Therefore, administration of oxygen has been used and ventilation has been assisted as needed in cases of 1,3-butadiene poisoning.

3.11.2 Reducing Body Burden

No information is available regarding displacing or removing absorbed 1,3-butadiene prior to metabolism to reactive metabolites.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Toxicity studies found mice to be extremely sensitive (DOE/NTP 1987b; Melnick et al. 1989, 1990b; NTP 1993). Studies on the metabolism of 1,3-butadiene demonstrated that the chemical is converted to its epoxy derivatives by P450 isoforms in lung, liver, kidney (see Section 3.4.3), and possibly other tissues. The epoxides may be responsible for most toxic and carcinogenic effects caused by 1,3-butadiene exposure. The epoxides are detoxified by hydrolysis or conjugation with glutathione (Kreiling et al. 1988). A higher rate of epoxide formation and a greater depletion of hepatic nonprotein sulfhydryl content in mice is probably responsible for their higher susceptibility to 1,3-butadiene toxicity. Since the macromolecular covalent binding is enhanced only after a substantial decrease of glutathione levels (Kreiling et al. 1988), sufficient availability of glutathione should mitigate the effects of 1,3-butadiene exposure.

Interference with the oxidative metabolism of 1,3-butadiene may also be effective in allowing pulmonary clearance of the parent compound to occur before reactive epoxides are formed. In mice, a 30–56% reduction in induction of erythrocyte micronuclei was observed in mice pretreated with various P450 inhibitors (Jackson et al. 2000b). However, the side effects of systemically inhibiting P450s in humans are unknown.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-butadiene 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 1,3-butadiene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of 1,3-Butadiene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,3-butadiene are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,3-butadiene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

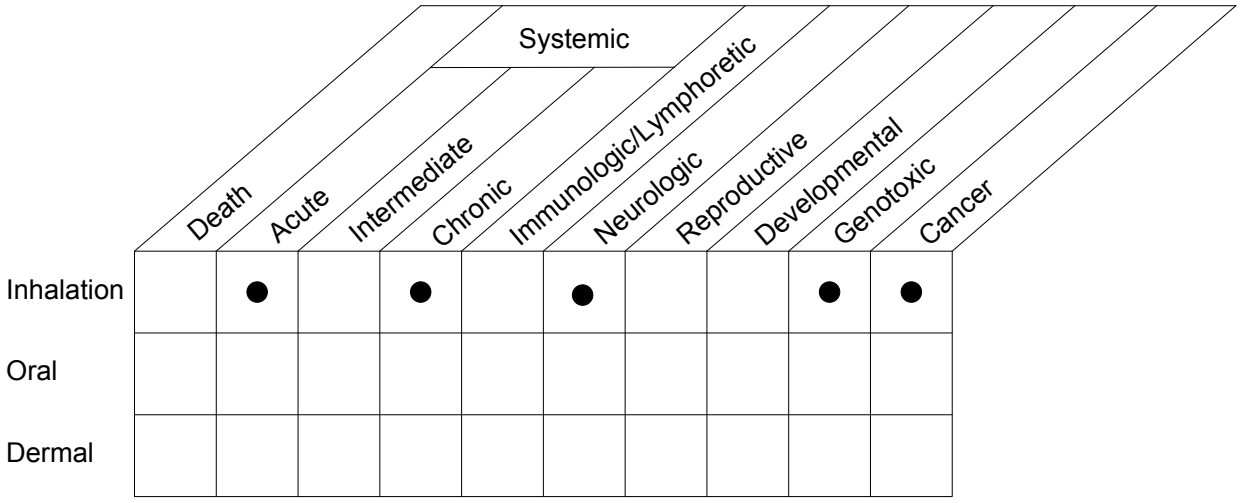
As seen from Figure 3-4, information regarding acute systemic effects (respiratory tract irritation and narcotic effect), chronic systemic effects (respiratory irritation), genotoxicity, and cancer exists for inhalation exposure in humans. No information was located regarding oral or dermal exposure of humans to 1,3-butadiene.

Inhalation studies in animals provide data on death, systemic effects, immunologic effects, neurologic effects, reproductive and developmental effects, genotoxicity, and carcinogenicity. No information was located regarding effects in animals after oral or dermal exposure to 1,3-butadiene.

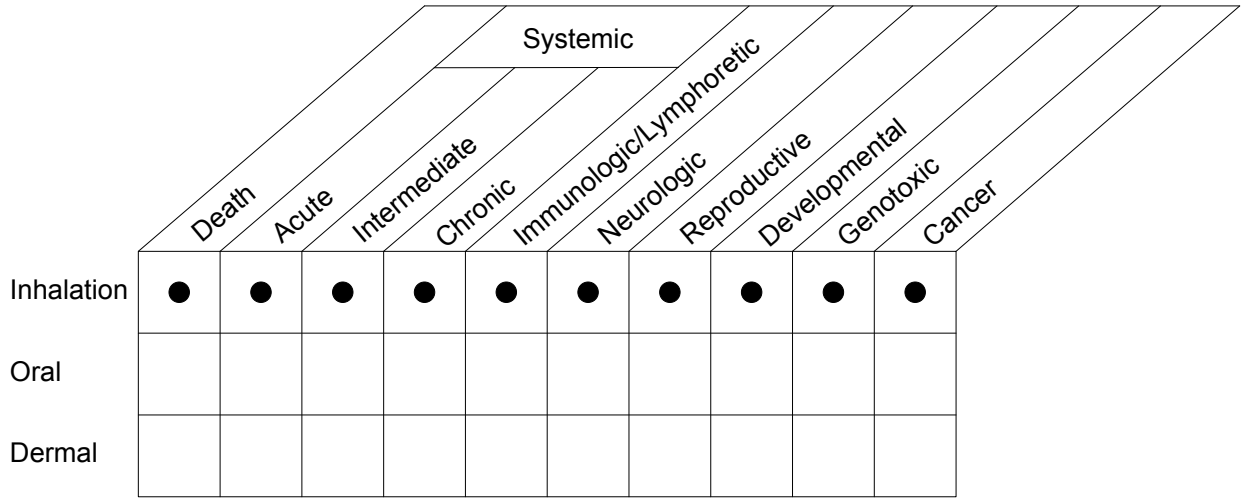
3.12.2 Identification of Data Needs

No studies were located regarding effects following oral or dermal exposure, and no pharmacokinetic studies by the oral or dermal routes were located; therefore, it is not possible to predict if effects

Figure 3-4. Existing Information on Health Effects of 1,3-Butadiene



Human



Animal

● Existing Studies

following oral or dermal exposure would be similar to those observed after inhalation exposure. Because 1,3-butadiene exists primarily as a gas and has been detected in soil off-gases at hazardous waste sites, inhalation exposure appears to be the greatest concern. However, it is not known if 1,3-butadiene is present in groundwater or soil at these hazardous waste sites because it is difficult to analyze these media for the compound. 1,3-Butadiene has been detected in industrial waste water and drinking water, and is poorly soluble in water (735 ppm). Therefore, oral and dermal routes of exposure cannot be ruled out. Information concerning 1,3-butadiene toxicity by these routes of exposure would be useful.

Acute-Duration Exposure. Acute inhalation exposure to very high concentrations (>25,000 ppm) of 1,3-butadiene may lead to narcosis and death by respiratory paralysis in animals (Carpenter et al. 1944). Data in humans are limited to a study of two men exposed to various concentrations of 1,3-butadiene for 6–8 hours that examined clinical signs and psychomotor function (Carpenter et al. 1944). No studies were located that correlated the level of exposure with the first signs of toxicity in humans or animals. Developmental effects were seen in mice after exposure to concentrations as low as 40 ppm (DOE/NTP 1987b; Irvine 1981). Although the available animal data identify critical targets of toxicity following acute-duration inhalation exposure, the database lacks adequate toxicokinetic and PBPK modeling data, which could be used to account for species differences in the metabolism of 1,3-butadiene; thus, an acute-duration MRL was not derived. Additionally, there are limited data on the potential effects of the parent compound, such as neurotoxicity, which may be a more sensitive target of toxicity in humans. Because people living at or near these hazardous waste sites may be exposed for brief periods of time, more dose-response data for acute exposures by oral and inhalation routes is considered to be important.

Intermediate-Duration Exposure. No information is available regarding effects of 1,3-butadiene during intermediate-duration exposure in humans. No studies were located regarding effects in humans or animals following oral or dermal exposure to 1,3-butadiene, and pharmacokinetic data for these routes of exposure are insufficient to predict whether the disposition or toxicity of 1,3-butadiene following oral or dermal exposure would be similar to that following inhalation exposure. Therefore, information regarding the toxicity of 1,3-butadiene by the oral route of exposure would be useful. Several studies on intermediate-duration inhalation exposure to 1,3-butadiene have been conducted in animals (Anderson et al. 1996, 1998; Crouch et al. 1979; Irons et al. 1986a; NTP 1984, 1993; Thurmond et al. 1986). Atrophy of reproductive organs, anemia, precancerous hyperplasia in multiple organs, and cancer occurred in mice exposed to ≥200 ppm (Irons et al. 1986a; NTP 1984, 1993). The observed hematological changes (macrocytic megaloblastic anemia) were similar to those found in human preleukemic syndrome (Biemer 1983), suggesting that 1,3-butadiene exposure might interfere with normal bone marrow cell

development. Further investigation of this topic could be valuable since epidemiological studies in humans indicate that hematopoietic tissue may be a possible target for 1,3-butadiene toxicity (Checkoway and Williams 1982). Several studies have identified potential targets of toxicity following intermediate-duration exposure; however, the available toxicokinetic and PBPK modeling data do not allow for adequate adjustment for species differences in the metabolism of 1,3-butadiene. Thus, intermediate-duration inhalation MRLs were not derived.

Chronic-Duration Exposure and Cancer. Possible risk for hematological disorders was reported in humans after chronic inhalation exposure to 1,3-butadiene in occupational settings, but exposure levels are lacking, and exposure to other chemicals occurs in these settings (Checkoway and Williams 1982). However, other studies (Cowles et al. 1994; Tsai et al. 2005) that monitored 1,3-butadiene levels have not found hematological alterations. Well-conducted inhalation studies identified respiratory effects, liver necrosis, gonadal atrophy, multi-site cancer, and increased mortality in mice at exposures as low as 6.25 ppm (Melnick et al. 1989, 1990a; NTP 1984, 1993), while renal pathology, cancer, and increased mortality were observed in rats exposed to ≥1,000 ppm (Owen et al. 1987). Because a serious LOAEL of severe ovarian atrophy (with complete destruction of oocytes, follicles, and corpora lutea) was found at 6.25 ppm, with no associated NOAEL, no chronic MRL has been derived. Chronic-duration studies are needed that identify a NOAEL in mice for gonadal atrophy. Oral studies are lacking, and toxicokinetic data are insufficient to predict toxicity across routes of exposure. Therefore, information concerning the possible toxicity of 1,3-butadiene by this route would be useful to identify the target organs and the thresholds for toxic effects.

Epidemiological studies in humans indicate a possible increase in risk of leukemia from occupational exposure to 1,3-butadiene (Cheng et al. 2007; Delzell et al. 1996; Divine 1990; Divine and Hartman 2001; Divine et al. 1993; Downs et al. 1987; Macaluso et al. 1996; Matanoski and Schwartz 1987; Matanoski et al. 1982, 1989a, 1989b, 1990; McMichael et al. 1974, 1975, 1976; Meinhardt et al. 1982; Ward et al. 1995). This is supported by the information about mutagenic activity of 1,3-butadiene metabolites (de Meester 1988) and by well-conducted chronic inhalation studies that provide information on carcinogenic effects of 1,3-butadiene in mice and rats (Melnick et al. 1989; NTP 1984, 1993; Owen et al. 1987). IARC (2009) and EPA (EPA 2002; IRIS 2012) concluded that there is sufficient evidence for the carcinogenicity of 1,3-butadiene in animals. IARC has classified 1,3-butadiene in group 1, carcinogenic to humans. EPA has classified 1,3-butadiene as a human carcinogen. The Department of Health and Human Services (NTP 2011) also identified 1,3-butadiene as a “known human carcinogen”. Further epidemiological investigations that examined additional potential targets of 1,3-butadiene toxicity

would be useful. Also, data are needed on 1,3-butadiene exposure to urban populations living in close proximity to major roadways and intersections, as well as on long-term follow-up of health effects, particularly the detection of diminishment in reproductive capability and prevalence of lympho-hematopoietic cancers.

No chronic oral or dermal carcinogenicity studies in animals were located, and pharmacokinetic data are insufficient to predict a carcinogenic potential of 1,3-butadiene by these routes.

Genotoxicity. Studies of chromosomal aberrations, sister chromatid exchanges, and *hprt* mutation frequencies among petrochemical and 1,3-butadiene monomer workers exposed to low levels (≤2 ppm) provide conflicting results (Albertini et al. 2001, 2007; Ammenheuser et al. 2001; Hayes et al. 1996, 2000; HEI 2003; Lovreglio et al. 2006; Sram et al. 1998; Tates et al. 1996; Ward et al. 1996, 2001; Zhou et al. 1986). 1,3-Butadiene has caused increases in micronuclei induction, chromosomal aberration frequency, and mutations of proto-oncogenes in *in vivo* studies of rats and mice following inhalation exposure (Autio et al. 1994; Cochrane and Skopek 1993; Cunningham et al. 1986; Irons et al. 1987b; Jauhar et al. 1988; Meng et al. 1999, 2000, 2004, 2007; Recio et al. 1992; Sills et al. 2001; Tice et al. 1987; Vodicka et al. 2006). Information on the genotoxic effects of 1,3-butadiene was also obtained from *in vitro* studies in prokaryotic (Arce et al. 1989; de Meester 1988, de Meester et al. 1980; Victorin and Stahlberg 1988) and eukaryotic (Cochrane and Skopek 1993; Sasiadek et al. 1991) organisms. These data sufficiently characterize the mutagenic potential of 1,3-butadiene metabolites.

Reproductive Toxicity. The atrophy of gonads in mice after chronic inhalation exposures as low as 6.25 ppm 1,3-butadiene was reported (Melnick et al. 1989; NTP 1984, 1993). The fertility of rats, guinea pigs, or rabbits was reported to be unaltered by acute- and intermediate-duration inhalation exposure to 1,3-butadiene (Anderson et al. 1996, 1998; Carpenter et al. 1944). Sperm head abnormalities were found in male mice exposed to 1,3-butadiene by inhalation (DOE/NTP 1988b). Further information regarding the reproductive effects of 1,3-butadiene in animals such as multigeneration studies would be useful to estimate the possible risk for reproductive effects in humans. An epidemiological study among exposed populations concentrating on reproductive effects would be useful.

No studies were located regarding reproductive toxicity of 1,3-butadiene by the oral or dermal routes in humans or animals, and pharmacokinetic data were insufficient to suggest the potential for 1,3-butadiene to cause reproductive effects by these routes of exposure. The potential for exposure of humans by the oral and dermal routes, however, is not known.

Developmental Toxicity. No information on developmental toxicity in humans was located. A developmental study by the inhalation route indicated growth retardation in rat fetuses and an increase in major skeletal abnormalities at a concentration of 1,000 ppm of 1,3-butadiene (Irvine 1981). Furthermore, fetotoxicity was observed in mice at acute-duration exposures of 40 ppm and intermediate-duration exposures of 12.5 ppm 1,3-butadiene (DOE/NTP 1987b). More data on developmental toxicity in other species (at least one of them nonrodent) would be useful to identify the possible developmental risk for humans. The developmental effects following other routes of exposure have not been studied, and pharmacokinetic data are insufficient to predict that responses would be similar to those by the inhalation route. Therefore, studies of oral exposures in animals to determine the possible developmental effects of 1,3-butadiene and the thresholds for these effects would be useful.

Immunotoxicity. Reduction in thymus weight and lymphoid histopathology was seen after the intermediate-duration exposure of mice to ≥625 ppm 1,3-butadiene (NTP 1993; Thurmond et al. 1986). The indications of disturbances in hemato- and lymphatopoietic stem cell regulations were observed after inhalation exposure of mice to 1,3-butadiene (Liederman et al. 1986). The high incidence of lymphoma among mice after the chronic exposure (NTP 1984, 1993) also indicates that the immune system is a target. A battery of immune function tests has not been performed in humans or animals. More data regarding humans and animals would be useful for determining potential human immunotoxicity of 1,3-butadiene. Studies regarding skin sensitization with 1,3-butadiene are lacking.

Neurotoxicity. Narcosis has been demonstrated in animals after acute inhalation exposure to very high levels of 1,3-butadiene (250,000 ppm) (Carpenter et al. 1944). No reliable information was located regarding neurotoxicity due to chronic inhalation exposure or to oral or dermal exposure for any duration. Information regarding early, subtle signs of possible neurological effects with correlation to the exposure levels is lacking. A battery of neurological and neurobehavioral tests would be useful to better define the neurological end points.

Epidemiological and Human Dosimetry Studies. Several epidemiological studies on health effects of 1,3-butadiene have been conducted (Case and Hosker 1954; Fox et al. 1974; Matanoski and Schwartz 1987; Matanoski et al. 1989a, 1989b; McMichael et al. 1974, 1975, 1976; Meinhardt et al. 1982). The limitation of these studies is that the cohorts of exposed workers were recruited from the rubber industry, in which the people were exposed to a mixture of various chemicals. Some genotoxicity studies have been conducted among 1,3-butadiene manufacturing workers and petrochemical workers

exposed to low (≤2 ppm) exposures, but have reported conflicting results (Albertini et al. 2001, 2007; Ammenheuser et al. 2001; Hayes et al. 1996, 2000; HEI 2003; Kelsey et al. 1995; Lovreglio et al. 2006; Tates et al. 1996; Ward et al. 1996, 2001; Wickliffe et al. 2009; Zhou et al. 1986). Reliable dosimetry data on the exposed populations would be useful for good epidemiological comparisons. Efforts to improve estimates of past exposures and to more accurately define current exposure levels to 1,3-butadiene would be valuable. Epidemiological studies should concentrate on the possible carcinogenic effect of 1,3-butadiene in humans and on changes in hemato- and lymphatopoietic systems as possible targets for 1,3-butadiene induced toxicity. The data obtained from workers exposed occupationally to low concentrations of 1,3-butadiene could possibly be extrapolated to populations living near hazardous waste sites.

Biomarkers of Exposure and Effect.

Exposure. The determination of 1,3-butadiene-derived urinary metabolites (Albertini et al. 2001, 2007; Ammenheuser et al. 2001; Bechtold et al. 1994; Dahl et al. 1990; Hayes et al. 1996, 2000; Sapkota et al. 2006; Ward et al. 1994, 1996), DNA adducts (Kreiling et al. 1986b; Sun et al. 1989b; Zhao et al. 2001), and hemoglobin adducts (Albertini et al. 2001, 2007; Begemann et al. 2001a, 2001b; Boogaard et al. 2001b; Hayes et al. 2000; HEI 2000; Osterman-Golkar et al. 1996) of rats, mice, and humans exposed to 1,3-butadiene has been performed. Data are needed that accurately correlate the level of biomarkers measured in the body, particularly for *pyr*-Val hemoglobin adducts with the exposure to 1,3-butadiene, as well as the variability in this correlation between sexes and ethnicity.

Effect. Conflicting data exist for the sensitivity of human lymphocyte *hprt* mutation frequencies resulting from occupational exposures (Albertini et al. 2001, 2007; Ammenheuser et al. 2001; Hayes et al. 1996, 2000; HEI 2003; Kelsey et al. 1995; Lovreglio et al. 2006; Tates et al. 1996; Ward et al. 1996, 2001; Wickliffe et al. 2009; Zhou et al. 1986). In mice and rats, levels of DEB-specific DNA-DNA cross-links correlated well with 1,3-butadiene inhalation and relative sensitivity of female mice to toxicity (Goggin et al, 2009). Two biomarkers for carcinogenic effect have been consistently found in multiple tumors sites in rodent chronic bioassays. A number of malignant gliomas and neuroblastomas in mice chronically inhaling 1,3-butadiene exhibited mutations of the p53 gene and H- and K-ras oncogenes (Kim et al. 2005), which have also been observed in forestomach tumors (Sills et al. 2001), hemagiosarcomas (Hong et al. 2000), and lymphomas (Zhuang et al. 1997) of chronically exposed mice. Data for reliable and specific biomarkers indicating onset of developmental effects in animals would be useful to determine if comparable exposure may lead to these effects in humans.

Absorption, Distribution, Metabolism, and Excretion. The timecouse of 1,3-butadiene and its primary metabolite, EB, in human blood has been investigated in volunteers inhaling 2 ppm for 20 minutes (Lin et al. 2001). *In vitro* studies have characterized some of the metabolism dynamics of 1,3-butadiene in animals (Bolt et al. 1983; Csanady et al. 1992; Duescher and Elfarra 1994; Elfarra et al. 1996, 2001; Himmelstein et al. 1994, 1995; Jackson et al. 2000a; Kreiling et al. 1987; Laib et al. 1990; Malvoisin and Roberfroid 1982; Malvoisin et al. 1979; Schmidt and Loeser 1985, 1986; Thornton-Manning et al. 1995b, 1997). Several toxicokinetic studies on 1,3-butadiene metabolism *in vivo* have been conducted in rats and mice following inhalation exposure (Bolt et al. 1983; Bond et al. 1987; Himmelstein et al. 1994; Kohn and Melnick 2001; Kreiling et al. 1986b; Shugaev 1969), but not following exposure by other routes. Thus, further studies in animals by the oral route to determine possible target organs by this route could be useful. Ethical considerations limit the testing of humans, but the development of methods to determine urinary and breath excretion of 1,3-butadiene and its metabolites by humans with known exposure to 1,3-butadiene may provide a means of monitoring humans for exposure.

Comparative Toxicokinetics. The study by Schmidt and Loeser (1985) indicated that there is a difference between the capability of mouse and rat liver postmitochondrial fractions to produce 1,2-epoxybutene-3 after incubation with 1,3-butadiene. Furthermore, monkey and human postmitochondrial liver preparations catalyzed the formation of only a small amount of the epoxide. Higher levels of the toxic epoxides were found in blood of mice following 1,3-butadiene exposure as compared to monkeys (Bolt et al. 1983; Csanady et al. 1992; Dahl et al. 1990; Duescher and Elfarra 1994; Elfarra et al. 1996, 2001; Jackson et al. 2000a; Sun et al. 1989a). Species differences in the toxicokinetics of a chemical may account for differences in toxic responses. Analysis of the blood, breath, and urine of humans exposed to 1,3-butadiene for parent compound and metabolites over time would provide a greater knowledge of the human metabolic pathways. Qualitative and quantitative comparison of human metabolites with those of animals could help identify the most appropriate species to serve as a model for predicting toxic effects and mechanisms of action in humans.

Methods for Reducing Toxic Effects.

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

The sensitivity of children to 1,3-butadiene toxicity, if any, is unknown. In mice, acute- and intermediate-duration inhalation exposures resulted in *in utero* fetal effects at exposure levels of 21.5–40 ppm (Anderson et al. 1996; DOE/NTP 1987b). No information is available for interfering with effects of 1,3-butadiene toxicity *in utero*.

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

3.12.3 Ongoing Studies

The following ongoing studies were identified in the Federal Research in Progress database (FEDRIP 2009).

E. Struble is being funded by EPA National Health and Environmental Effects Research Laboratory (HEERL) to use environmental irradiation chambers (smog chambers) to induce the natural photochemically stimulated transformations of environmental pollutants. The synthetic urban smog mixture is composed of 55 hydrocarbon species representative of the ambient air of an average city in the United States. In this study, A549 cells were exposed simultaneously to irradiated and non-irradiated chamber mixtures for 5 hours. Post exposure, adverse health effects were determined by measures of increased cellular stress cytokine release and cytotoxicity. Exposure to the photochemically-generated products of 1,3-butadiene, toluene, and methanol induced increases in both cytotoxicity and IL-8 gene expression compared to 1,3-butadiene, toluene, or methanol alone. The exposure design was used to investigate the toxicity of chemicals after photochemical reactions and interactions with the urban atmosphere on healthy and susceptible individuals using representative *in vitro* samples. This research informs the toxicity from exposures to multiple environmental pollutants found in urban settings.

James A. Swenberg is being funded by the National Institute of Environmental Health Sciences (NIEHS) to examine the molecular dose of previously unexplored DNA adducts in rodents exposed to 1,3-butadiene and 3-butene-1,2-diol (BD-diol). The data will be compared with mutation frequencies and mutational spectra to determine (1) if a particular adduct could be used as a mutagenic indicator, and (2) to determine the effects of exposure on gene expression. First, it will be determined if hydroxymethylvinyl ketone (HMVK) is formed in vivo during exposure to 1,3-butadiene and BD-diol in a sex-, species-, and exposure concentration-dependent manner, resulting in mutagenicity. Secondly,

promutagenic N1 adenine adducts will be observed to see if they are converted to more stable inosine adducts, which may accumulate in tissues during chronic exposures. Several specific aims will be accomplished while addressing these questions. Specific Aim 1 is to examine the formation of potentially mutagenic DNA adducts (specifically 1, N2-propanodeoxyguanosine) by HMVK *in vivo*. Specific Aim 2 is to determine the utility of the N-terminal valine adduct of HMVK (HMVK-Val) as a biomarker of HMVK formation by BD and BD-diol. Specific Aim 3 is to develop methods for detecting N1- inosine, N1- and N6-adenine adducts derived from BD metabolites in vivo. Specific Aim 4 is to determine the mutagenic responses induced by BD exposures and characterize the impact of BD-diol-derived metabolites on the spectra of mutations induced by BD exposure in the B6C3F1 mouse and F344 rat to identify which adducts studied in Aims 1 and 3 are quantitative indicators of mutagenesis. Specific Aim 5 will examine the effects of exposure to BD and BD-diol on gene expression and DNA repair pathways. Collectively, these experiments have been designed to inform on adduct formation, DNA repair, mutagenicity, and genomic alterations in rodents exposed to 1,3-butadiene and BD-diol, as well as the impact of glutathione depletion and DNA repair deficiency.

Elaine Symanski is being funded by the National Cancer Institute (NCI) to evaluate an association between lymphohematapoietic (LH) cancer incidence and air pollution in the Houston metropolitan area, with particular emphasis on three compounds: benzene, 1,3-butadiene, and styrene. Data from the Texas Cancer Registry (TCR) from 1995 to 2005 and the Texas Commission on Environmental Quality (TCEQ) from 1992 to 2003 will be analyzed to: (1) investigate the spatial and temporal distribution of LH cancer incidence in Harris and surrounding counties; (2) evaluate the association between distance from industrial sources and LH cancer incidence; (3) identify optimal methods for assessing ambient levels of benzene, 1,3-butadiene, and styrene using existing TCEQ monitoring data; and (4) evaluate the association between ambient levels of benzene, styrene, and 1,3-butadiene and LH cancer incidence using Poisson regression in single and multi-pollutant models. This will be the first study to examine this association in Harris and seven surrounding counties (Texas) and is among the first to utilize monitored levels of HAPs to assess increased risks of LH cancer associated with air pollution. This work will also correlate cancer rates with proximity to industrial facilities as well as ambient levels of benzene, styrene, and 1,3-butadiene. This study will address a gap in the literature by examining the association between HAPs and cancer incidence in Harris County, Texas and will further explore innovative methods to evaluate this association utilizing existing data sources.

Natalia Y. Tretyakova is being funded by the National Cancer Institute to evaluate the role of DNA-DNA cross-linking in the genotoxicity of diepoxybutane and 1,3-butadiene. DEB-DNA cross-links will be

structurally characterized and formation sequence preferences will be determined. The hydrolytic stability of DEB-DNA cross-links will be evaluated for their recognition by the *E. coli* UvrABC repair complex. DEB-DNA cross-links in rodent tissues will be quantified by capillary high performance liquid chromatography-electrospray tandem mass spectrometry (HPLC-ESI-MS/MS) methods. This research will provide valuable information on the molecular mechanisms underlying the genotoxic activity of diepoxybutane.

4. CHEMICAL AND PHYSICAL INFORMATION

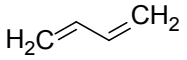
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of 1,3-butadiene is located in Table 4-1. This information includes synonyms, chemical formula and structure, and identification numbers.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of 1,3-butadiene is located in Table 4-2.

Table 4-1. Chemical Identity of 1,3-Butadiene[a]

Characteristic	Information
Chemical name	1,3-Butadiene
Synonyms and trade names	Butadiene; buta-1,3-diene; biethylene; bivinyl; divinyl; vinylethylene; erythrene; alpha,-gamma-butadiene; pyrrolylene[b]
Chemical formula	C_4H_6
Chemical structure	
Identification numbers:	
CAS registry	106-99-0
NIOSH RTECS	EI9275000[c]
EPA hazardous waste	R0377-0754[d]
DOT/UN/NA/IMDG shipping	1010
EINECS	203-450-8
HSDB	181
NCI	C50602

[a]All information obtained from HSDB 2009 and ChemID Plus Advanced 2009 except where noted.
[b]O'Neil et al. 2006.
[c]NIOSH 2005.
[d]Miller 1978.

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

Table 4-2. Physical and Chemical Properties of 1,3-Butadiene

Property	1,3-Butadiene	Reference
Molecular weight	54.09	O'Neil et al. 2006
Color	Colorless	Lewis 2007
Physical state	Gas	Lewis 2007
Melting point	-108.966 °C	O'Neil et al. 2006
Boiling point	-4.5 °C	O'Neil et al. 2006
Density:		
at 25 °C (g/cm^3)	0.6149	Lide 2008
Vapor density	1.88 (air=1)	NIOSH 2005
Odor	Mildly aromatic; gasoline-like	Lewis 2007
Water	Not applicable[a]	Amoore and Hautala 1983
Air	1.6 ppm	Amoore and Hautala 1983
Odor threshold		
Solubility:		
Water at 25 °C	735 mg/L	McAuliffe 1966
Organic solvent(s)	Soluble in ether, ethanol and benzene; very soluble in acetone	Lide 2008
Partition coefficients:		
Log K_{ow}	1.99	Hansch et al. 1995
K_{oc}	288 (estimated)[b]	HSDB 2009
Vapor pressure at 25 °C	$2.11x10^3$ mm Hg	AIChE 2000
Henry's law constant at 25 °C	$7.4x10^{-2}$ atm-m^3/mol (estimated)[c]	HSDB 2009
Autoignition temperature	414 °C	Lewis 2007
Flashpoint	-76 °C	Lewis 2007
Explosive limits	2.0-11.5%	O'Neil et al. 2006
Conversion factors	1 ppm=2.21 mg/m^3 1 mg/m^3=0.452 ppm	NIOSH 2005

[a]Amoore and Hautala (1983) reported an odor threshold of 0.0014 ppm for 1,3-butadiene in water; however, these authors state that this solution lacks enough persistence for this value to be used for reference purposes.
[b]This K_{oc} value was estimated using the measured log K_{ow} value (1.99) and a regression derived equation.
[c]This Henry's Law constant value was calculated from the measured vapor pressure ($2.11x10^3$ mm Hg at 25 °C) and water solubility (735 mg/L).

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

5.1 PRODUCTION

1,3-Butadiene was discovered in the nineteenth century and its use in the development of rubber-like polymers was explored during the early 1900s (Grub and Loser 2005; Sun and Wristers 2002). Large volume production of 1,3-butadiene in the United States began during World War II as a result of the nation's synthetic rubber program (American Chemical Society 2007; Dolnick and Potash 1948). U.S. production rose to 2.7 billion pounds in 1965 as new plants were started to meet the increasing butadiene-rubber demand of the auto industry (Chemical Market Reporter 2006; Grub and Loser 2005; Kirshenbaum 1978). Production reached 3.7 billion pounds (1,674 metric tons) by 1974 and then fluctuated through the 1980s as a response to market pressures (Grub and Loser 2005; Kirshenbaum 1978; Sun and Wristers 2002). Production growth resumed during the 1990s, reaching 4.5 billion pounds (2,020 metric tons) in 1998 (Grub and Loser 2005). Actual production volumes of 1,3-butadiene manufactured in the United States during more recent years are not available; however, the annual U.S. production capacity was reported to be 6 billion pounds (2,800 metric tons) during 2008 (Chemical Week 2008; SRI 2008).

The 1,3-butadiene market is heavily dependent on the synthetic rubber demand of the auto industry, which accounts for approximately 60% of the total consumption of this substance (Chemical Market Reporter 2006). Also, since most 1,3-butadiene is produced through steam cracking, the supply of this chemical has been largely influenced by the demand for ethylene, the primary product from steam cracking (Sun and Wristers 2002).

The companies that produced 1,3-butadiene in the United States, their production sites, and their annual capacities during 2008 (the most recent year for which figures are available) are shown in Table 5-1 (SRI 2008). Table 5-2 summarizes the number of facilities in each state that manufactured or processed 1,3-butadiene in 2007, the ranges of maximum amounts on site, if reported, and the activities and uses as reported in the Toxics Release Inventory (TRI) (TRI09 2011). The data listed in this table should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Except for a small amount of 1,3-butadiene produced by the oxydehydrogenation of n-butene, all the 1,3-butadiene produced in the United States is a co-product of ethylene manufacture (Chemical Market Reporter 2006; Sun and Wristers 2002). In this process, feed streams ranging from light hydrocarbons to heavy gas oils are cracked in the presence of steam at 700–900 °C (Grub and Loser 2005; Kirshenbaum

Table 5-1. Companies that Produce 1,3-Butadiene in the United States and Annual Capacities During 2008

Company	Location	Capacity (million pounds/year)	Capacity (metric tons)
Equistar Chemicals, LP	Alvin, Texas	150	68,060
	Channelview, Texas	865	392,500
	Corpus Christi, Texas	200	90,740
ExxonMobil Chemical Company	Baton Rouge, Louisiana	385	
	Baytown, Texas	325	147,500
INEOS Americas, LLC			
INEOS Olefins & Polymers USA	Alvin, Texas	235	106,600
Sabina Petrochemicals LLC	Port Arthur, Texas	900	
Shell Chemical LP	Deer Park, Texas	360	163,300
	Norco, Louisiana	575	260,900
Texas Petrochemicals, Inc.	Houston, Texas	1,080	490,000
	Port Neches, Texas	925	419,700
Total		6,000	2,722,000

Source: SRI 2008

Table 5-2. Facilities that Produce, Process, or Use 1,3-Butadiene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	8	0	9,999,999	1, 3, 5, 6, 8, 13, 14
AR	6	1,000	999,999	1, 2, 3, 6, 9, 12
AZ	1	10,000	99,999	9
CA	73	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
CO	13	0	9,999,999	1, 3, 5, 6, 8, 12, 13
CT	3	1,000,000	9,999,999	2, 3, 6
DE	11	1,000	9,999,999	1, 2, 3, 5, 6, 7, 9, 12, 13
GA	4	100,000	9,999,999	1, 5, 6
HI	7	1,000	99,999	1, 3, 5, 6, 13, 14
IA	5	100,000	9,999,999	1, 3, 4, 5, 6
IL	39	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14
IN	24	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 12, 13, 14
KS	11	0	499,999,999	1, 3, 6, 10, 13
KY	16	10,000	9,999,999	1, 3, 4, 5, 6, 7, 9, 12, 13
LA	106	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MI	28	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
MN	10	0	9,999,999	1, 2, 3, 5, 6, 7, 12, 13
MO	6	0	9,999	1, 5, 7, 12, 14
MS	12	1,000	499,999,999	1, 2, 3, 4, 5, 6, 7, 9, 13, 14
MT	19	100	999,999	1, 3, 5, 6, 8, 12, 13, 14
NC	9	0	49,999,999	2, 3, 6, 7, 8, 10
ND	4	0	9,999	1, 2, 3, 4, 6
NE	2	0	9,999	3, 8, 11, 12
NH	1	1,000	9,999	6
NJ	16	0	99,999	1, 3, 4, 5, 6, 7, 12, 13
NM	2	0	9,999	1, 3, 5, 7, 11
NY	7	10,000	999,999	2, 3, 4, 6, 8, 11
OH	33	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
OK	21	0	9,999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
PA	20	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 12, 13, 14
PR	1	10,000,000	49,999,999	1, 5, 7
SC	3	0	99,999	1, 5, 6, 13, 14
TN	21	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14
TX	234	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	15	100	999,999	1, 3, 4, 5, 6, 7, 8, 9, 12
VA	7	0	9,999	1, 3, 4, 5, 6, 13
VI	5	100	99,999	1, 2, 3, 6, 13
WA	27	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use 1,3-Butadiene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WI	2	100,000	9,999,999	6
WV	10	0	99,999,999	1, 5, 6, 7, 8, 12
WY	5	0	99,999	1, 3, 4, 6

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

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

Source: TRI09 2011 (Data are from 2009)

1978; Sun and Wristers 2002). The fraction of 1,3-butadiene produced by this process varies widely with the type of feedstock used and is lowest with low-boiling input streams (Grub and Loser 2005; Kirshenbaum 1978).

Purification of the crude C4 stream resulting from the steam cracking process cannot be achieved by a simple distillation due to the close boiling point of the various products and the fact that 1,3-butadiene forms an azeotrope with butane (Grub and Loser 2005; Kirshenbaum 1978). 1,3-Butadiene can be removed from the hydrocarbon stream by liquid-liquid extraction or extractive distillation. The selective solvents used in these processes include aqueous cupric ammonium acetate, acetonitrile, furfural, dimethylformamide, N,N-dimethylacetamide, and N-methylpyrrolidinone (Grub and Loser 2005; Sun and Wristers 2002).

The oxidative dehydrogenation of n-butene, used in the production of 1,3-butadiene, is a highly selective, irreversible process that involves heating the starting material, air, and a suitable catalyst together at 400–450 °C (Grub and Loser 2005; Kirshenbaum 1978; Sun and Wristers 2002). The hydrogen released in the dehydrogenation step combines with oxygen, producing large amounts of heat, which makes this process energy-efficient (Grub and Loser 2005; Kirshenbaum 1978; Sun and Wristers 2002). As indicated above, oxidative dehydrogenation of n-butene has not been competitive with the steam cracking process for manufacture of 1,3-butadiene (Chemical Market Reporter 2006; Grub and Loser 2005). Rather, this method has been used on a campaign basis when there is a large enough differential between feedstock and 1,3-butadiene prices (Grub and Loser 2005).

5.2 IMPORT/EXPORT

Large amounts of 1,3-butadiene are imported into the United States as consumption typically exceeds production (Chemical Market Reporter 2006; Chemical Week 2008; Sun and Wristers 2002). U.S. imports of 1,3-butadiene in 2005 were approximately 600 million pounds (Chemical Market Reporter 2006). More recent import data are not available. U.S. Exports of 1,3-butadiene are considered to be negligible (Chemical Market Reporter 2006).

5.3 USE

1,3-Butadiene is used as a monomer in the production of rubber and plastics; approximately 60% of the 1,3-butadiene consumed in the United States is used in the production of synthetic rubbers (Chemical Market Reporter 2006). 1,3-Butadiene uses can be broken down into the following categories: synthetic

rubber, 61% (styrene butadiene rubber [SBR], 30%; polybutadiene elastomer, 25%; polychloroprene elastomer, 4%; nitrile elastomer, 2%) adiponitrile/hexamethylene diamine (HMDA), 11%; styrene-butadiene latex, 12%; ABS resins, 5%; and other uses, 11% (Chemical Market Reporter 2006). Automobile tires are the major end-use product (Chemical Market Reporter 2006). Both styrene butadiene rubber and polybutadiene are used heavily for this purpose. 1,3-Butadiene is also used for other automotive applications such as high-impact polystyrene and ABS resin plastics (Chemical Market Reporter 2006). 1,3-Butadiene is a precursor in the production of adiponitrile (used to make nylon) and chloroprene (used to make neoprene) (Chemical Market Reporter 2006).

5.4 DISPOSAL

The recommended method of disposal of 1,3-butadiene is by incineration within a suitable combustion chamber or in a safe area (HSDB 2009). Gaseous 1,3-butadiene can be burned directly; however, liquefied 1,3-butadiene (in a compressed cylinder) must be atomized before burning (HSDB 2009). Kennedy et al. (2009) report that burning off 1,3-butadiene, also referred to as flaring, is commonly practiced at facilities where excess amounts of this substance need to be destroyed (Kennedy et al. 2009).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,3-Butadiene has been identified in at least 13 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for 1,3-butadiene is not known. The frequency of these sites can be seen in Figure 6-1.

1,3-Butadiene is a high-volume, volatile hydrocarbon used in the production of commercial plastics and synthetic rubbers (Chemical Market Reporter 2006). The chemical reactivity of this monomer is utilized in its transformation into polymeric materials (Sigsby et al. 1987).

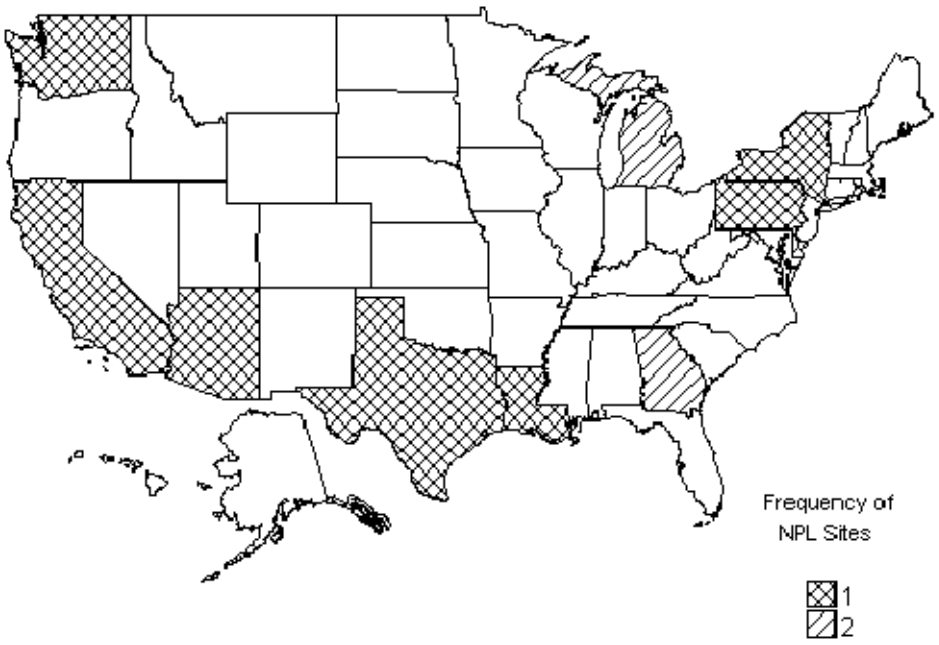
1,3-Butadiene may be released to the environment as an intentional or fugitive emission during its production, use, storage, transport, or disposal. Large amounts (1.17 million pounds) of this hydrocarbon are released to the atmosphere from commercial processes (TRI09 2011). Data on the detection of 1,3-butadiene in soil and water are scarce. In the past, it has been qualitatively detected in drinking water (EPA 1978; Kraybill 1980); however, more recent measurements are not available.

1,3-Butadiene is a highly volatile gas; therefore, it is expected to partition predominantly to the atmosphere. In the atmosphere, 1,3-butadiene is expected to undergo rapid destruction, primarily by photo-initiated reactions. The reaction with photochemically produced hydroxyl radicals has a calculated half-life of approximately 6 hours and is expected to be the dominant pathway for atmospheric removal (Atkinson 1989). Destruction of atmospheric 1,3-butadiene by the gas-phase reaction with tropospheric ozone and by the night-time reaction with nitrate radicals in urban areas is also expected to be significant (Atkinson and Carter 1984; Atkinson et al. 1984).

Limited data have been located on the fate of 1,3-butadiene in soil or water. Based on its physical properties, rapid volatilization of 1,3-butadiene from either soil or water to the atmosphere is expected to dominate over all other potential environmental processes. Based on estimated soil adsorption coefficient values, 1,3-butadiene is not expected to adsorb significantly to soil or sediment, nor is it expected to bioconcentrate in fish or aquatic organisms based on estimated bioconcentration and bioaccumulation factors.

Although 1,3-butadiene undergoes rapid photooxidation in the atmosphere, it is almost always present at very low concentrations in urban and suburban areas (Curren et al. 2006; Grant et al. 2007; Oguz et al.

Figure 6-1. Frequency of NPL Sites with 1,3-Butadiene Contamination



Derived from HazDat 2007

2003; Reiss 2006; Reiss and Griffin 2004; Sax et al. 2004). Automobile exhaust is a constant source of 1,3-butadiene release to the atmosphere. Because of the compound's ubiquity in the urban/suburban atmosphere, the general population is exposed to low ppb levels of 1,3-butadiene through inhalation (Higashino et al. 2007; Hughes et al. 2003). Exposure to 1,3-butadiene may also occur from the inhalation of cigarette smoke or the smoke from wood fires (Adam et al. 2006; Bartle et al. 1969; Blomberg and Widmark 1975; Brunnemann et al. 1990; Carmella et al. 2009; Counts et al. 2006; Gustafson et al. 2007; Lofroth et al. 1989; Pankow et al. 2004, 2007; Penn and Snyder 2007; Stump et al. 1989; Thweatt et al. 2007; Vainiotalo et al. 2008). Ingestion of contaminated food or drinking water may also lead to low levels of exposure, although current levels of this compound in food and water samples are not known, nor is there a good understanding of their frequency of detection (EPA 1978; Hughes et al. 2003; Kraybill 1980; Leber 2001; McNeal and Breder 1987; Startin and Gilbert 1984). The levels of 1,3-butadiene in soil are not known. Elevated levels of exposure for the general population may occur for those near its site of manufacture or facilities where it is made into polymeric materials.

Occupational exposure to 1,3-butadiene is expected to be limited to those working at facilities that manufacture 1,3-butadiene or convert it into commercial polymers (Anttinen-Klemetti et al. 2006; Begemann et al. 2001a; Fustinoni et al. 2004; Jones and Harris 1983; Lovreglio et al. 2006; Meinhardt et al. 1982; Sathiakumar et al. 2007; Tsai et al. 2001, 2005; Ward et al. 2001). Exposure by inhalation is expected to be the dominant pathway for exposure. Dermal exposure to liquified 1,3-butadiene could occur during an explosion of a pressurized storage tank or some other catastrophic event.

6.2 RELEASES TO THE ENVIRONMENT

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

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

6.2.1 Air

Estimated releases of 1.17 million pounds (530 metric tons) of 1,3-butadiene to the atmosphere from 193 domestic manufacturing and processing facilities in 2009 accounted for about 99% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). These releases are summarized in Table 6-1.

The dominant sources for the release of 1,3-butadiene to the atmosphere are fugitive or accidental emissions during its manufacture, use, transport, and storage. Low levels of 1,3-butadiene are continuously emitted to the atmosphere from many sources including exhaust from motor vehicle engines using petroleum-based fuels.

EPA's National Emission Inventory database (NEI) contains detailed information about sources that emit criteria air pollutants and their precursors, and hazardous air pollutants for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emission data for 1,3-butadiene in 2005 is presented in Table 6-2 and suggest that automobile usage accounts for approximately one-third of all emissions.

1,3-Butadiene was measured in the exhaust of typical automobiles and light trucks using both winter and summer gasoline formulations and accounted for up to 0.12% of total hydrocarbon emissions (Stump et al. 1989). An earlier study determined that the concentration of 1,3-butadiene in automobile exhaust was 20–60 ppb (Neligan 1962). 1,3-Butadiene has also been detected in the exhaust of diesel engines (Hayano et al. 1985) and high-altitude jet aircraft engines operating under simulated conditions (Katzman and Libby 1975).

There are several minor sources for the release of 1,3-butadiene to the atmosphere, all of which involve the thermal breakdown of other materials. 1,3-Butadiene has been detected as a component of the sidestream smoke from cigarettes (Adam et al. 2006; Bartle et al. 1969; Blomberg and Widmark, 1975; Carmella et al. 2009; Penn and Snyder 2007; Vainiotalo et al. 2008). The average amount of 1,3-butadiene in sidestream cigarette smoke is 205–361 µg/cigarette (Brunnemann et al. 1990), with an average airborne yield of 400 µg/cigarette (Lofroth et al. 1989).

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,3-Butadiene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	3,069	0	0	47	0	3,069	47	3,116
AR	1	1,140	0	0	0	0	1,140	0	1,140
AZ	1	1,460	0	0	0	0	1,460	0	1,460
CA	17	6,116	0	0	8	0	6,116	8	6,124
CO	3	776	0	0	0	0	776	0	776
CT	1	32	0	0	0	0	32	0	32
DE	1	534	0	0	0	0	534	0	534
GA	2	3,732	0	0	0	0	3,732	0	3,732
HI	1	401	0	0	0	0	401	0	401
IA	1	4,766	0	0	0	0	4,766	0	4,766
IL	7	43,415	10	0	44	0	43,425	44	43,469
IN	5	3,859	5	0	0	0	3,864	0	3,864
KS	3	120	0	0	0	0	120	0	120
KY	5	15,246	0	0	726	0	15,246	726	15,972
LA	23	110,511	574	0	65	0	111,085	65	111,150
MI	2	3,585	0	0	0	0	3,585	0	3,585
MN	1	3,983	2	0	0	0	3,985	0	3,985
MS	1	809	0	0	0	0	809	0	809
MT	3	903	0	0	0	0	903	0	903
NC	3	858	0	0	0	0	858	0	858
ND	1	89	0	0	0	0	89	0	89
NJ	4	102	0	0	0	0	102	0	102
OH	13	35,145	6	0	4,161	5	39,311	6	39,317
OK	4	6,981	0	0	0	0	6,981	0	6,981
PA	4	2,258	0	0	0	0	2,258	0	2,258
SC	1	5,520	0	0	0	0	5,520	.	5,520
TN	4	4,648	0	0	0	0	4,648	0	4,648
TX	67	902,132	49	2,266	10	6	904,446	17	904,463
UT	2	1,069	0	0	0	0	1,069	0	1,069
VA	1	962	0	0	0	0	962	0	962
VI	1	1,039	0	0	0	0	1,039	0	1,039
WA	4	292	0	0	0	0	292	0	292
WI	1	156	0	0	0	0	156	0	156
WV	1	2,100	0	0	13	0	2,113	0	2,113

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,3-Butadiene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	2	500	0	0	0	0	500	0	500
Total	193	1,168,307	646	2,266	5,074	11	1,175,391	913	1,176,304

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

RF = reporting facilities; UI = underground injection

Source: TRI09 2011 (Data are from 2009)

Table 6-2. 1,3-Butadiene Emission Data for 2005[a]

Category name	Type	Annual emissions (tons)	Percentage
Fuel comb, residential fireplaces	Nonpoint	3,352.17	6.35
On-road vehicles, gasoline	Onroad	16,008.77	30.32
Miscellaneous sources	Nonpoint	17,627.65	33.39
On-road vehicles, diesel	Onroad	1,058.86	2.01
Agricultural field burning	Nonpoint	339.31	0.64
Fuel comb, residential woodstoves	Nonpoint	315.31	0.60
Graphic arts	Point	0.00	0.00
Gas stations	Point	0.01	0.00
Wildfires	Nonpoint	3,340.53	6.33
Bulk gasoline terminals	Point	5.11	0.01
Fuel comb, commercial/institutional	Nonpoint	0.07	0.00
Planes, trains, and ships	Nonroad	109.07	0.21
Prescribed fires	Nonpoint	164.95	0.31
Industrial process, storage and transfer	Nonpoint	2.61	0.00
Industrial process, NEC	Point	129.88	0.25
Surface coating, industrial	Point	16.81	0.03
Non-road equipment, diesel	Nonroad	364.74	0.69
Non-road equipment, gasoline	Nonroad	8,062.72	15.27
Industrial process, petroleum refineries	Nonpoint	1.30	0.00
Industrial process, petroleum refineries	Point	22.15	0.04
Industrial process, cement manufacturing	Point	64.37	0.12
Logging slash burning	Nonpoint	211.34	0.40
Fuel comb, electric utility	Point	2.30	0.00
Waste disposal, open burning	Point	0.03	0.00
Waste disposal, open burning	Nonpoint	123.52	0.23
Fuel comb, commercial/institutional	Point	0.78	0.00
Industrial process, oil and gas production	Point	7.71	0.01
Waste disposal	Nonpoint	1.52	0.00
Industrial process, chemical manufacturing	Point	603.65	1.14
Degreasing	Point	0.01	0.00
Industrial process, chemical manufacturing	Nonpoint	1.44	0.00
Solvent, NEC	Point	0.24	0.00
Planes, trains, and ships	Point	323.90	0.61
Fuel comb, industrial boilers, ICEs	Nonpoint	2.86	0.01
Fuel comb, industrial boilers, ICEs	Point	111.72	0.21
Waste disposal	Point	37.16	0.07
Industrial process, oil and gas production	Nonpoint	0.18	0.00
Industrial process, storage and transfer	Point	217.59	0.41

Table 6-2. 1,3-Butadiene Emission Data for 2005[a]

Category name	Type	Annual emissions (tons)	Percentage
Industrial process, pulp and paper	Point	0.30	0.00
Industrial process, metals	Point	161.81	0.31

[a]Emission estimates are subject to updates for subsequent revised versions of the 2005 National Emissions Inventory data. These numbers may be different than values published for previous versions of the 2005 data and may also be different than values for subsequent revisions of the data as generated by EPA.

ICEs = internal combustion engines; NEC = not elsewhere classified

Source: EPA 2008

The burning of plastics or rubber has been shown to release small amounts of 1,3-butadiene (Miller 1978). In a test designed to simulate a real-life electrical overload condition, 1,3-butadiene was detected when polyurethane coated wire was heated to 250 °C for 40 minutes (Rigby 1981). 1,3-Butadiene has also been measured as a component of the smoke from brush fire (Stephens and Burleson 1969), and as a stack emission from waste incinerators (Junk and Ford 1980). The concentrations of 1,3-butadiene were not presented in these studies. The mean, minimum, and maximum concentrations of 1,3-butadiene measured in the air of nine municipal structural fires were 1.03, 0.03, and 4.84 ppm, respectively (Austin et al. 2001). The sources of 1,3-butadiene were considered to be both the combustion of wood and the thermal degradation of polymeric materials. Forest fires are considered to be a natural source of 1,3-butadiene in the atmosphere (Curren et al. 2006). Detection of 1,3-butadiene while heating rapeseed oil indicates that the heating of cooking oils may be a source of 1,3-butadiene in indoor air (Pellizzari et al. 1995).

1,3-Butadiene has been identified in air samples collected at 8 of the 13 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.2.2 Water

Estimated releases of 646 pounds (0.29 metric tons) of 1,3-butadiene to surface water from 193 domestic manufacturing and processing facilities in 2009, accounted for about 0.05% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). An additional 913 pounds (0.08 metric tons) were transferred off-site which includes releases to publicly owned treatment works (POTWs) (TRI09 2011). These releases are summarized in Table 6-1.

Additional information regarding the release of 1,3-butadiene to water was not located in the available literature. 1,3-Butadiene has been identified in groundwater samples collected at 1 of the 13 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007). It was not identified in surface water at any of the NPL sites.

6.2.3 Soil

Estimated releases of 5,074 pounds (2.3 metric tons) of 1,3-butadiene to soils from 193 domestic manufacturing and processing facilities in 2009, accounted for about 0.43% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). An additional

2,266 pounds (1.03 metric tons), constituting about 0.19% of the total environmental emissions, were released via underground injection (TRI09 2011). These releases are summarized in Table 6-1.

Additional information regarding the release of 1,3-butadiene to soil was not located in the available literature. 1,3-Butadiene has been identified in soil samples collected at 2 of the 13 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007). It was not identified in sediment at any of the NPL sites.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

1,3-Butadiene's high volatility suggests that it will partition predominantly to the atmospheric compartment, where it is not expected to be adsorbed to particulate matter to any significant extent (Eisenreich et al. 1981).

Based on the calculated Henry's Law constant of $7.4x10^{-2}$ atm-m^3/mol, the half-life for volatilization of 1,3-butadiene is 2.2 hours from a model river (1 m deep, flowing at 1 m/second, with a wind velocity of 3 m/second) and 2.9 days from a model lake (1 m deep, flowing at 0.05 m/second, with a wind velocity of 0.5 m/second) (Lyman et al. 1990). Based on an experimental log octanol/water partition coefficient of 1.99 (Hansch et al. 1995), a calculated soil adsorption coefficient of 288 (Lyman et al. 1990) suggests that adsorption to sediment and suspended organic matter will not be a significant fate process. From the log octanol/water partition coefficient, a calculated bioconcentration factor of 19 (Lyman et al. 1990) indicates that 1,3-butadiene will not bioconcentrate in fish and aquatic organisms to any significant extent. However, no experimental data have been located to verify these theoretical values.

If released to soil, 1,3-butadiene is expected to volatilize rapidly from either moist or dry soil to the atmosphere. This follows from the estimated lack of any appreciable adsorption to soil, and consideration of 1,3-butadiene's calculated Henry's law constant for moist soil or its vapor pressure, 2,100 mm Hg at 25 °C (AIChE 2000), for dry soil. Both values suggest a rapid rate of volatilization from their respective media.

The calculated soil adsorption coefficient of 288 (Hansch et al. 1995; Lyman et al. 1990) suggests that 1,3-butadiene may display moderate mobility in soil (Swann et al. 1983). However, the expected rapid rate of volatilization and the possibility of rapid degradation in soil suggest that there is little potential for

1,3-butadiene to leach into groundwater. But until adequate groundwater monitoring for 1,3-butadiene has been performed, the partitioning of 1,3-butadiene in soil cannot be adequately addressed.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Butadiene is a reactive, electron-rich chemical that is expected to undergo rapid reactions with the electrophilic oxidants typically present in the atmosphere: ozone, photochemically produced hydroxyl radicals, nitrate radicals, and molecular oxygen. Among these, the most rapid reaction in the atmosphere is with photochemically produced hydroxyl radicals.

The atmospheric degradation of 1,3-butadiene by photo-initiated processes has been established empirically by early studies. These studies typically involved irradiating urban air samples in atmospheric chambers of varying complexity and monitoring the disappearance of each constituent. Using this technique, 1,3-butadiene, at an average concentration of 12.4 ppb, disappeared in 6 hours when irradiated with natural sunlight during October (Kopczynski et al. 1972). In another study, a half-life of 2 hours was determined for the atmospheric removal of 1,3-butadiene using natural sunlight in October or November (Altshuller et al. 1970). In smog chamber studies, the sunlight oxidation of 1,3-butadiene led to the formation of fairly potent eye irritants, suggesting destruction of this compound with concomitant formation of oxygenated species (Dimitriades et al. 1975; Heuss and Glasson 1968). It is believed that the destruction of 1,3-butadiene occurs by photo-initiated bimolecular processes rather than direct photochemical degradation (Kopczynski et al. 1972). It is important to note that the rate of destruction of 1,3-butadiene when it was irradiated with natural light depended on the time of day in which the irradiation occurred. Furthermore, these studies were performed in October and November, when the amount and the intensity of available sunlight is diminished over that of summer months; thus, these values probably represent the high end of the compound's atmospheric lifetime. The individual processes responsible for the destruction of 1,3-butadiene in the atmosphere are discussed below.

Numerous studies have determined the rate constant for the gas-phase reaction of 1,3-butadiene with photochemically produced hydroxyl radicals (Atkinson 1985; Atkinson and Aschmann 1984; Atkinson et al. 1977, 1979; Maldotti et al. 1980). The experimental rate constant 6.85×10^{-11} cm^3/molecule-second at 26 °C (Atkinson et al. 1977) is representative. Given an average hydroxyl radical concentration of 5×10^5 molecule/cm^3 (Atkinson 1985), the half-life for this second-order process is 5.6 hours. Major products of this reaction include acrolein and formaldehyde (Baker et al. 2005).

Gas-phase 1,3-butadiene also reacts with ozone in the atmosphere. Rate constants ranging from $6.7x10^{-18}$ to $8.4x10^{-18}$ cm^3/molecule-second at 25 °C have been published in the literature (Atkinson and Carter 1984; Jaspar et al. 1974). Using an average atmospheric ozone concentration of $7x10^{11}$ molecules/cm^3 (Atkinson and Carter 1984), half-lives ranging from 1.4 to 1.7 days can be calculated for this second-order process. Therefore, the reaction of 1,3-butadiene with ozone is expected to contribute to the overall destruction of atmospheric 1,3-butadiene. The initial products from the reaction of 1,3-butadiene with ozone are acrolein, formaldehyde, acetylene, ethylene, and formic anhydride (Niki et al. 1983). All of these products are susceptible to secondary reactions with ozone and other atmospheric oxidants.

The night-time degradation of 1,3-butadiene is also expected to occur via the gas-phase reaction with nitrate radicals; this tends to be significant in urban areas, where the concentration of this oxidant is typically higher than in rural areas (Altshuller and Cohen 1964; Gay and Bulfalini 1971; Maldotti et al. 1980). A rate constant of $5.4x10^{-14}$ cm^3/molecule-second at 22 °C has been determined for this reaction. This corresponds to a half-life of 14.9 hours using an average atmospheric nitrate radical concentration of $2.4x10^8$ molecule/cm^3 (Atkinson et al. 1984), typical of mildly polluted urban centers. Acrolein has been identified as a primary product of this reaction.

In summary, there are three gas-phase pathways that degrade 1,3-butadiene in the troposphere. Depending on local conditions, any one or all of these reactions may occur. Destruction of atmospheric 1,3-butadiene by the gas-phase reaction with photochemically produced hydroxyl radicals is expected to be the dominant photo-initiated pathway. Degradation via nitrate radicals is expected to be a significant night-time process in urban areas.

6.3.2.2 Water

Data on the degradation of 1,3-butadiene in aquatic systems are limited. Experimental data are restricted to microbial degradation studies performed under aerobic conditions. The bulk of these data were obtained from isolated bacterial strains (pure cultures), not with mixed microbial populations typically found in natural systems, and are not considered to be representative of the biodegradation of 1,3-butadiene in the environment. However, results from these studies suggest that biodegradation of 1,3-butadiene proceeds through oxidation to form 3,4-expoxybutene (Hou et al. 1979, 1980, 1983; Patel et al. 1982a; Watkinson and Somerville 1976). Watkinson and Somerville (1976) reported further degradation.

6.3.2.3 Sediment and Soil

As is the case for the degradation of 1,3-butadiene in water, very limited data on the destruction of this compound in soil could be located in the available literature. Results from pure culture studies suggest a similar aerobic biodegradation pathway for 1,3-butadiene in soil compared to the pathway in water (Hou et al. 1979; Patel et al. 1979, 1982a, 1982b; VanGinkel et al. 1987; Watkinson and Somerville 1976).

6.3.2.4 Other Media

Specific information regarding the transformation or degradation of 1,3-butadiene in other environmental media was not located.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,3-butadiene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,3-butadiene in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,3-butadiene 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 1,3-butadiene in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

1,3-Butadiene is widely detected at low ppb levels in urban air samples. Reported average concentrations range from 0.1 to 2 $\mu g/m^3$ (0.04–0.9 ppb) (Curren et al. 2006; Grant et al. 2007; Oguz et al. 2003; Reiss 2006; Reiss and Griffin 2004; Sax et al. 2004). A major source of 1,3-butadiene in urban air is automobile engine exhaust (Broderick and Marnane 2002; Sigsby et al. 1987; Stump and Dropkin 1985; Stump et al. 1989). Atmospheric emissions from industrial facilities that produce or use 1,3-butadiene are another major source of the compound in areas located near these facilities. Concentrations as high as 40 $\mu g/m^3$ (18 ppb) have been measured in the air near industrial sites (highest 24-hour level measured downwind from a major industrial source) (Grant et al. 2007). Curren et al. (2006) analyzed 3,267 air samples collected at eight rural locations in Canada and reported a mean 1,3-butadiene concentration of 0.02 $\mu g/m^3$ (0.009 ppb) at these sites. EPA (2003a) estimated that the average background concentration of 1,3-butadiene in the air of the United States is 0.13 $\mu g/m^3$ (0.058 ppb). McCarthy et al. (2006)

provided a lower estimate (<0.02 μg/m^3; 0.009 ppb) of 1,3-butadiene in the background air of North America. Table 6-3 lists reported concentrations of 1,3-butadiene measured in outdoor air.

1,3-Butadiene has also been detected in indoor air samples. Mean concentrations of 1,3-butadiene measured in indoor air of homes in New York were 1.0 μg/m^3 (0.5 ppb) during the winter and 1.2 μg/m^3 (0.54 ppb) during the summer (Sax et al. 2004). In Los Angeles, mean concentrations were 0.5 μg/m^3 (0.2 ppb) during the winter and 0.2 μg/m^3 (0.09 ppb) during the fall. The concentrations of 1,3-butadiene measured in a tavern were 11 and 19 μg/m^3 (5.0 and 8.6 ppb) in two separate studies, while the outside air concentration was ≤1 μg/m^3 (0. 5 ppb) at the same time (Lofroth et al. 1989). The difference in the indoor versus outdoor concentration may be ascribed to the presence of 1,3-butadiene in cigarette smoke. The concentration of 1,3-butadiene in a smoke-filled bar was 2.7–4.5 μg/m^3 (1.2–2.0 ppb) (Brunnemann et al. 1990). Higher 1,3-butadiene levels have been observed in air samples collected from the smoking areas of restaurants and pubs than in air samples collected from the nonsmoking areas of these buildings (Kim et al. 2001; Vainiotalo et al. 2008). Mean 1,3-butadiene concentrations measured in the indoor air of 32 smoking homes and 32 nonsmoking homes were 1.7 and 0.5 μg/m^3 (0.77 and 0.23 ppb), respectively (Kim et al. 2001). Mean 1,3-butadiene levels were 0.31–0.38 μg/m^3 (0.14-0.17 ppb) in the air of wood burning homes and 0.114 μg/m^3 (0.0515 ppb) in non-wood burning homes in Hagfors, Sweden (Gustafson et al. 2007). Table 6-4 lists reported concentrations of 1,3-butadiene measured in indoor air.

6.4.2 Water

No current information on the occurrence of 1,3-butadiene in water was located in the available literature.

1,3-Butadiene was found in 1 of 204 water samples taken in 1975–1976 from surface waters near known industrialized areas across the United States. The single positive sample was obtained in the Carquinez Strait, Posta Corta, California, at an approximate concentration of 2 ppb (Ewing et al. 1977).

No specific data on its presence in drinking water, such as monitoring dates or concentration, were located; however, 1,3-butadiene has been qualitatively detected in U.S. drinking water in the past (EPA 1978; Kraybill 1980).

6.4.3 Sediment and Soil

No data on the occurrence of 1,3-butadiene in soil were located in the available literature.

Table 6-3. 1,3-Butadiene Concentrations in Outdoor Air

Location	Concentration (µg/m^3)						Reference
	n	>LOD	LOD	Mean	Median	Maximum	
Urban							
New York City							Sax et al. 2004
Winter	31	14%	0.06	0.1	ND	0.7	
Summer	27	11%	0.06	0.1	ND	2.0	
Los Angeles							Sax et al. 2004
Winter	35	24%	0.06	0.2	ND	1.7	
Fall	32	3%	0.06	0.01	ND	0.3	
Houston							Reiss 2006
16 Locations	4,374	61%	0.02[a]	1.3	—	7.2	
Texas							Grant et al. 2007
47 Urban/ industrial sites	—	<30–74%	0.61	0.5	—	40	
Baltimore							Sapkota and Buckley 2003
Toll booth	56	100%	0.46	—	2–13.5[b]	19	
Baltimore							Kim et al. 2007
Parking garage	24[c]	—	—	—	0.2–0.5[d]	8	
Canada							Curren et al. 2006
30 Locations	5,160	—	0.001–0.02	0.22	0.17	2.58	
Rural							
Canada							Curren et al. 2006
8 Locations	3,267	—	0.001–0.02	0.02	—	—	
Background estimate							
United States	—	—	—	0.13	0.10	2.2	EPA 2003a
North America	—	—	—	<0.02	<0.02	<0.02	McCarthy et al. 2006

[a]Value is referred to as the reporting limit.
[b]Lower and upper median values correspond to measurements taken during 12–3 a.m. and 6–9 a.m., respectively.
[c]Seven-hour samples were collected on 18 week days and 6 weekend days.
[d]Lower and upper median values correspond to measurements taken on weekends and weekdays, respectively.

LOD = limit of detection; n = number of samples; ND = not detected

Table 6-4. 1,3-Butadiene Concentrations in Indoor Air

Location	Concentration ($\mu g/m^3$)						Reference
	n	>LOD	LOD	Mean	Median	Maximum	
New York City							Sax et al. 2004
Winter	36	64%	0.06	1.0	0.7	5.8	
Summer	30	44%	0.06	1.2	ND	12	
Los Angeles							Sax et al. 2004
Winter	40	60%	0.06	0.5	0.5	1.8	
Fall	32	38%	0.06	0.2	ND	1.5	
Arizona NHEXAS							Gordon et al. 1999
Home indoor	24	4%	0.38	ND	ND	0.6	
Home outdoor	14	0%	0.38	ND	ND	ND	
Ottawa, Canada							Graham et al. 2004
House background	17	65%	0.1	0.51	0.36	1.63	
Cold-start house[a]	17	100%	0.1	5.76	2.69	28.6	
Cold-start garage[a]	17	100%	0.1	82.8	84.7	166	
Birmingham, United Kingdom							Kim et al. 2001
6 smoking homes	32	100%	0.11	1.7	0.7	10.8	
6 nonsmoking homes	32	<100%	0.11	0.5	0.4	1.1	
Restaurants	6	—	0.11	1.5	—	—	
Pubs	6	—	0.11	3.0	—	—	
Other indoor[b]	43	—	0.11	0.2–0.9	—	—	
Helsinki, Finland							Vainiotalo et al. 2008
10 Restaurants							
Smoking area	20	100%	0.02	4.3	—	10.1	
Non-smoking area	20	100%	0.02	1.1	—	3.9	
Hagfors, Sweden							Gustafson et al. 2007
Wood burning homes	14	NR	0.03–0.15	0.31–0.38	0.20–0.23	0.90–1.54[c]	
Reference homes	10	NR	0.03–0.15	0.11	0.10–0.11	0.18–0.24[c]	
Area outdoor	9	NR	0.03–0.15	0.12	0.11	—	

[a]Concentrations measured in the house and garage after a cold vehicle engine was started in the attached garage.
[b]Includes offices, department stores, cinemas, perfume shop, libraries, and laboratories.
[c]90^{th} percentile values.

LOD = limit of detection; n = number of samples; ND = not detected; NHEXAS = National Human Exposure Assessment Survey; NR = not reported

6.4.4 Other Environmental Media

1,3-Butadiene is used to manufacture synthetic rubber and plastics that are frequently used for food packaging. Because residual 1,3-butadiene may be present in the polymers used to make the containers, both the packaging and the food contained therein have been analyzed. In one study, 1,3-butadiene at a concentration of 8–9 ng/g (ppb) was detected in three of three brands of olive oil packaged in 1,3-butadiene rubber-modified acrylonitrile-acrylic bottles (McNeal and Breder 1987). Analysis of the bottles themselves found 1,3-butadiene residues as high as 6,600 ng/g (ppb). Soft-plastic packaging tubs used as containers for potato salad, cottage cheese, and yogurt had residual 1,3-butadiene levels in the range of 21–1,700 ng/g (ppb). However, no 1,3-butadiene was detected in any of the food packed in these containers (detection limit 1 ppb). Chewing gum made with a 1,3-butadiene rubber base did not show residual traces of this diene (McNeal and Breder 1987). Soft-plastic margarine tubs from five major name brands in the United Kingdom contained 1,3-butadiene residues ranging from 5 to 310 µg/kg (ppb), but none of the monomer was detected in the margarine samples themselves (detection limit 0.2 µg/kg) (Startin and Gilbert 1984). The authors concluded that migration of the 1,3-butadiene monomer from plastic packaging to food is unlikely to present a problem. Residual levels of 1,3-butadiene in food containers are closely regulated by the Food and Drug Administration.

Pellizzari et al. (1995) measured 0.1 mg of 1,3-butadiene in rapeseed oil emissions during 20 minutes of heating the oil in a wok at 260 °C. The presence of 1,3-butadiene was attributed to the pyrolytic decomposition of unsaturated fatty acids in the oil.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

1,3-Butadiene is almost always present in the air at low levels due to its emission from motor vehicles. Therefore, the general population is probably routinely exposed to ppb levels of this compound. Exposure to 1,3-butadiene by the general population is expected to be dominated by inhalation (Higashino et al. 2007; Hughes et al. 2003). Reported mean concentrations of 1,3-butadiene measured in urban air generally range from 0.1 to 2 µg/m^3 (0.4–0.9 ppb) (Curren et al. 2006; Grant et al. 2007; Oguz et al. 2003; Reiss 2006; Reiss and Griffin 2004; Sax et al. 2004). Sapkota et al. (2006) measured mean 1,3-butadiene personal air exposure levels of 1.22 µg/$m^{3.}$ (0.55 ppb) for suburban-weekend exposure, 1.47 µg/m^3 (0.66 ppb) for urban-week day exposure, and 2.88 µg/m^3 (1.3 ppb) for tollbooth worker exposure in the Baltimore, Maryland area.

Inhalation of 1,3-butadiene by the general population may also occur due to other sources. 1,3-Butadiene has been identified in cigarette smoke; therefore, smokers and those nearby are exposed to this compound (Adam et al. 2006; Bartle et al. 1969; Blomberg and Widmark 1975; Brunnemann et al. 1990; Carmella et al. 2009; Counts et al. 2006; Lofroth et al. 1989; Pankow et al. 2004, 2007; Penn and Snyder 2007; Thweatt et al. 2007; Vainiotalo et al. 2008). Reported delivery levels of 1,3-butadiene in the mainstream smoke of cigarettes range from 1.3 to 100 μg/cigarette (Pankow et al. 2004; Thweatt et al. 2007). Nazaroff and Singer (2004) calculated a 1,3-butadiene inhalation intake of 16–37 μg/day for nonsmokers who live with a smoker. This value was based on an exposure relevant emission factor of 515 μg 1,3-butadiene/cigarette and a 1,3-butadiene exposure concentration of 1.4–3.1 μg/m^3 (Nazaroff and Singer 2004). Counts et al. (2006) measured 1,3-butadiene concentrations ranging from 11.2 to 59.3 μg/cigarette in the mainstream smoke of 26 different commercial cigarettes sold in the United States.

1,3-Butadiene is present in the smoke from brush fires, wood fires, and municipal structural fires (Austin et al. 2001; Gustafson et al. 2007; Stephens and Burleson 1969), suggesting that inhalation of the smoke from wood fires will lead to low-level exposure to 1,3-butadiene. Gustafson et al. (2007) reported a mean 1,3-butadiene concentration of 0.33 μg/m^3 (0.15 ppb) in the personal air of individuals living in wood-burning homes and 0.14 μg/m^3 (0.063 ppb) in the personal air of a reference group. Its presence in waste incinerator emissions (Junk and Ford 1980) suggests that exposure to the general population may occur for those living nearby. Small amounts of 1,3-butadiene are produced by the thermal degradation of polyurethane-coated wire, an event that may occur during an electrical overload (Rigby 1981). The thermal degradation of other 1,3-butadiene-based plastics or rubbers may produce 1,3-butadiene (Miller 1978), also leading to low-level exposure of the general population by inhalation.

If the mean daily urban air concentration of 1,3-butadiene is 0.29 ppb (0.64 μg/m^3), as determined in an analysis and compilation of experimental reports of ambient monitoring data obtained from 1970 to 1987 (Shah and Heyerdahl 1988), a nonoccupational daily intake of 12.8 μg per person can be obtained based on an average human intake of 20 m^3 air/day. Marshall et al. (2006) calculated a 1,3-butadiene intake rate of 7.3 μg/day based on an exposure concentration of 0.55 μg/m^3 and a mean breathing rate of 13.1 m^3/day. Kim et al. (2002) measured mean personal air exposure concentrations of 1.1 μg/m^3 (0.50 ppb) during the night time and 0.8 μg/m^3 (0.36 ppb) during the day time for 12 residents of Birmingham, United Kingdom who were nonsmokers.

No data are available that quantify general population exposure to 1,3-butadiene by other routes of intake, such as ingestion of contaminated drinking water. Low-level exposure by ingestion of contaminated

drinking water may occur as 1,3-butadiene has been qualitatively detected in U.S. drinking water supplies (EPA 1978; Kraybill 1980). Given that residues of 1,3-butadiene have been found in plastic and rubber food containers and in a few samples of the food contained in these containers (McNeal and Breder 1987), very low-level exposure to the general population may occur by ingestion of contaminated foods packaged in these containers (Hughes et al. 2003; Leber 2001). Leber (2001) estimated an upper-bound 1,3-butadiene intake of 44 ng/day from food contact sources which include styrene butadiene rubber-containing chewing gum, polymeric coatings, closures with sealing gaskets, and other indirect additives.

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1980 and 1983, 9,456 workers, of which 286 are women, were estimated to be exposed to 1,3-butadiene (NIOSH 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any chemicals listed therein. These surveys provide only an estimate of the number of workers potentially exposed to chemicals in the workplace. During a study involving 13,130 men who had been employed for at least 1 year at any of eight synthetic rubber plants in the United States or one in Canada between 1943 and 1992, it was estimated that 10,429 (79%) of these individuals had occupational exposure to 1,3-butadiene (Delzell et al. 2001; Macaluso et al. 2004). Occupational exposure to 1,3-butadiene is expected to be limited to inhalation of this compound, although dermal contact with liquified 1,3-butadiene may occur during a large spill, tank explosion, pipeline rupture, or similar catastrophic event. Specific industrial classifications or job descriptions involving exposure to 1,3-butadiene are provided below.

Levels of 1,3-butadiene measured in the air at styrene-butadiene rubber (SBR) plants have been reported (Anttinen-Klemetti et al. 2006; Jones and Harris 1983; Meinhardt et al. 1982; Sathiakumar et al. 2007; Ward et al. 2001). Table 6-5 lists 1,3-butadiene air concentrations associated with typical SBR operations. These concentrations were measured in air samples collected at different times between 1977 and 1991 at a synthetic rubber plant in Canada (Sathiakumar et al. 2007). These data show that individuals directly involved in the production of styrene-butadiene rubber have the greatest exposure to 1,3-butadiene at these facilities, although high concentrations were also associated with some equipment maintenance and control technician operations as well. Air concentrations associated with tank farm and transfer pumphouse operations (mean, 103 mg/m^3; 56.6 ppm) were at least an order of magnitude greater than those of any of the other operations. Maximum concentrations measured at this facility were as high as 1,490 mg/m^3 (673 ppm).

Table 6-5. Air Concentrations of 1,3-Butadiene Corresponding to Typical Operations Within a Styrene-Butadiene Rubber (SBR) Plant[a]

Operation	n	Concentration (mg/m^3)			
		Mean	Median	Minimum	Maximum
SBR production					
Polymerization					
Tank farm, transfer pumphouse	231	103	33.1	0.13	1,490
Reactor, blowdown, panel board	261	9.9	2.2	0.04	146
Recovery, compressor house, high solids recovery	333	22.5	3.5	0.04	1,200
Unspecified operative	35	2.4	0.91	0.00	34.3
Coagulation, blending, solutions prep	314	2.1	0.44	0.04	42.0
Finishing					
Baler, packager, reclaim	111	0.64	0.33	0.07	4.2
Dryer, baler dryer	134	2.9	0.44	0.11	271
Unspecified operative	39	0.29	0.15	0.04	1.5
Maintenance, production, maintenance field					
Foreman, engineer	15	0.44	0.40	0.04	1.5
Instrument worker, meter person, electrician, maintenance inspector	56	4.9	0.42	0.04	108
Pipefitter, oiler, mechanic, blacksmith, boilermaker, outside machinist	250	9.7	1.8	0.04	234
Cleanup crew, laborer, work pool, utility person	74	3.1	1.1	0.11	40.0
Technical/lab					
Rubber control, technician	210	30.1	2.1	0.00	1,150
Butadiene control, hydrocarbon control, technician	41	4.9	0.15	0.00	67.4
Shipping/distribution					
Labor, utility person, service person	24	0.20	0.15	0.00	0.66
Utilities					
Copolymer effluent operative	103	1.3	0.88	0.00	17.5
Unspecified/miscellaneous operative	114	0.42	0.22	0.00	4.2

[a]Air samples were collected at different times at a Canadian synthetic rubber plant between 1977 and 1991.

Source: Sathiakumar et al. 2007

1,3-Butadiene has been measured in the air of petrochemical facilities (Begemann et al. 2001a; Fustinoni et al. 2004; Lovreglio et al. 2006; Tsai et al. 2001, 2005). Mean time-weighted average concentrations of 1,3-butadiene were 10.23 mg/m^3 (4.55 ppm) between 1979 and 1996 and 0.56 mg/m^3 (0.25 ppm) between 1997 and 2003 at the Deer Park and Norco Manufacturing complexes owned by Shell Oil Company (Tsai et al. 2005). Short-term exposures to this substance were as high as 987 mg/m^3 (439 ppm) in 1979–1996 and 337 mg/m^3 (150 ppm) in 1997–2003. The decline in 1,3-butadiene levels in air at these facilities in recent years is attributed to the implementation of new health standards in 1996 (Tsai et al. 2001, 2005). A walk-through survey of 11 monomers, 17 polymers, and 2 end-user plants found that personal exposures ranged from <0.006 ppm to 374 ppm (0.013-827 mg/m^3) (Fasen et al. 1990).

Two studies have reported levels of 1,3-butadiene measured in human blood, breath, and urine. Perbellini et al. (2003) measured average 1,3-butadiene concentrations of 1.0, 1.9, and 1.0 ng/L in the alveolar air, blood, and urine, respectively, of 46 forestry workers who were nonsmokers and 3.6, 11.4, and 3.9 ng/L in the alveolar air, blood, and urine, respectively, of 15 forestry workers who were smokers. The individuals had not been involved in forestry work for 2 months; therefore, occupational exposure was not considered to be a contributing factor. Fustinoni et al. (2004) measured end-shift 1,3-butadiene levels of 2.4, 3.8, and 4.3 ng/L in the exhaled air, urine, and blood, respectively, of 42 workers with a mean personal exposure of 11.5 µg/m^3 (5.20 ppb) and levels of 2.3, 3.1, and 5.9 ng/L in the exhaled air, urine, and blood, respectively, of 43 workers with a mean personal exposure of 0.9 µg/m^3 (0.4 ppb). Pre-shift levels in exhaled air and urine were 2.4 and 3.8 ng/L, respectively, for the higher exposed workers and below detection for the lower-exposed workers.

Other occupations where exposures to 1,3-butadiene may occur include petroleum refinery workers, professional bus, truck, and taxi drivers, parking garage attendants, tollbooth workers, and employees working in areas where smoking is permitted.

6.6 EXPOSURES OF CHILDREN

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

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults.

The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are expected to be exposed to 1,3-butadiene primarily through inhalation of low levels in air. Children who live near areas of heavy vehicle traffic or near industrial facilities where 1,3-butadiene is produced or used may be exposed to higher levels of 1,3-butadiene. The available data indicate that exposure to 1,3-butadiene through ingestion of food and drinking water is expected to be low relative to inhalation exposure. Biomonitoring data for children, including levels of 1,3-butadiene and its metabolites measured in breast milk, neonatal blood, cord blood, and meconium fluid have not been located in the available literature.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

High levels of exposure to 1,3-butadiene are likely to be limited to those resulting from an occupationally related use of this compound. Inhalation is the most likely route of high exposure to 1,3-butadiene. 1,3-Butadiene is stored and transported in pressurized tanks, and it is possible that high levels of exposure by inhalation or dermal contact with the liquified gas may occur during the loading and unloading of these tanks, or by the accidental rupture of these tanks. Occupations where potentially high exposures to 1,3-butadiene may occur include those in styrene-butadiene rubber facilities, those in petroleum refineries, professional bus, truck, and taxi drivers, parking garage attendants, tollbooth workers, and employees working in areas where smoking is permitted. Individuals who live near facilities where 1,3-butadiene is produced or used have the potential for high exposure to this substance. Individuals who are frequently exposed to smoke from combustion sources, such as firefighters, may have high exposures to 1,3-butadiene (Austin et al. 2001). Individuals living very close to high traffic roads may be exposed to higher levels of butadiene.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-butadiene is available. Where adequate information is not available, ATSDR, in conjunction with NTP is required to assure the initiation of a program of

research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-butadiene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of 1,3-butadiene are well documented (Amoore and Hautala 1983; Hansch et al. 1995; HSDB 2009; Lewis 2007; Lide 2008; McAuliffe 1966; O'Neil et al. 2006; NIOSH 2005), and its environmental fate can be estimated from these properties (Lyman et al. 1982). No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2009, became available in February of 2011. This database is updated yearly and should provide a list of industrial production facilities and emissions.

The trends in the production and use of 1,3-butadiene are well documented (Chemical Market Reporter 2006; Chemical Week 2008; Grub and Loser 2005; Kirshenbaum 1978; SRI 2008; Sun and Wristers 2002), and there do not appear to be any critical information gaps. 1,3-Butadiene monomer does not occur in most products used in the home, although residues of this compound in commercial packages, especially food containers (McNeal and Breder 1987), are not well described. It is clear that the majority of 1,3-butadiene is released to the atmosphere (TRI09 2011). The disposal of 1,3-butadiene appears to be a straightforward process (HSDB 2009). No data needs are identified.

Environmental Fate. The fate of 1,3-butadiene in the atmosphere is well understood (Atkinson 1985; Atkinson and Carter 1984; Atkinson et al. 1984; Kopczynski et al. 1972). The fate of 1,3-butadiene in soil and water is not well understood, and partitioning from these media has to be determined from the physical and chemical properties of this compound (Lyman et al. 1982). A reliable method capable of

detecting 1,3-butadiene in soil and water was not located in the available literature, and it is not clear whether 1,3-butadiene is absent from these media or simply not yet detected. The persistence of 1,3-butadiene in soil and water is not known, and the degree of partitioning from one environmental compartment to another can only be estimated. Exposure via ingestion or dermal contact to populations surrounding hazardous waste sites cannot, therefore, be accurately determined. Experimental data that address the partitioning of 1,3-butadiene in the environment, its potential to enter drinking water supplies, and its lifetime in soil and water are necessary to completely characterize the environmental fate of this compound.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 1,3-butadiene from air. No data on the bioavailability of 1,3-butadiene from other sources (water or soil, for example) were located in the available literature. In conjunction with the data needs for determining 1,3-butadiene in environmental media, bioavailability studies from environmental media would be useful.

Food Chain Bioaccumulation. In theory, 1,3-butadiene is not believed to bioconcentrate significantly in fish and aquatic organisms; thus, it is not expected to biomagnify in the food chain (Hansch and Leo 1995; Lyman et al. 1982). No data addressing this point, however, were located in the available literature. Validation of these theories by valid experimental studies will aid in establishing a quantitative determination of 1,3-butadiene exposure to the general public.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of 1,3-butadiene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,3-butadiene in the environment can be used in combination with the known body burden of 1,3-butadiene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Data on the levels of 1,3-butadiene in environmental media are limited. Extensive data on the occurrence of 1,3-butadiene in ambient air samples are available (Curren et al. 2006; Grant et al. 2007; Oguz et al. 2003; Reiss 2006; Reiss and Griffin 2004; Sax et al. 2004), but more data would be helpful. Data on the occurrence of 1,3-butadiene in water samples are very limited (Ewing et al. 1979). The presence of 1,3-butadiene in drinking water has been noted in the literature, but no concentrations or frequency of detection are available (EPA 1978; Kraybill 1980). The development of reliable analytical techniques for

the analysis of 1,3-butadiene in soil and water will establish unambiguously the levels at which this compound is found in environmental media.

Exposure Levels in Humans. Limited data on levels of occupational exposure to 1,3-butadiene were available in the literature; however, occupational exposure to this compound appears to be limited to a readily definable group of industrial classifications (NIOSH 1989; Sathiakumar et al. 2007). Exposure levels for the general population are not well defined. Studies that correlate personal exposure with daily activities are necessary to adequately establish exposure levels for 1,3-butadiene. Biological monitoring studies cannot be performed until acceptable experimental techniques are developed. Exposure levels for those living near hazardous waste sites are not available and should be established.

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

Exposures of Children. No information regarding exposures of children to 1,3-butadiene are currently available. Biomonitoring data for children, including levels of 1,3-butadiene and its metabolites measured in breast milk, neonatal blood, cord blood, and meconium fluid have not been located in the available literature. Studies are needed to help determine if there are differences between childhood and adult exposure to 1,3-butadiene.

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

Exposure Registries.

No exposure registries for 1,3-butadiene were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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.

6.8.2 Ongoing Studies

Ongoing studies related to the potential for human exposure to 1,3-butadiene were not located.

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1,3-butadiene, its metabolites, and other biomarkers of exposure and effect to 1,3-butadiene. 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.

7.1 BIOLOGICAL MATERIALS

No standardized method to test for the presence of 1,3-butadiene in biological materials presently exists. Only a limited number of techniques have been employed to measure this compound in biological materials.

Perbellini et al. (2003) have developed a method to measure unmetabolized 1,3-butadiene concentrations in human blood, urine, and exhaled air. Breath samples were collected by expiration into headspace vials. Venous blood samples with EDTA added as an anticoagulant or urine samples were injected into a glass tube. Samples were analyzed using gas chromatography-mass spectrometry (GC-MS). Reported detection limits for 1,3-butadiene were 0.5 ng/L in blood, 1 ng/L in urine, and 0.8 ng/L in alveolar air.

A technique for the determination of 1,3-butadiene in margarine samples was reported by Startin and Gilbert (1984). The margarine sample is placed in a vial, sealed, and heated to 70 °C where it is allowed to equilibrate for 1 hour. The amount of 1,3-butadiene in the sample is determined by withdrawing a headspace sample, and injecting it directly into a GC equipped with a MS detection system. Quantitation is obtained by comparison of the peak height to that of a standard of known concentration. The sensitivity of this method allows quantitation down to 0.001 mg/kg (1 ppb). A similar headspace technique was used to test for the presence of butadiene in olive oil, vegetable oil, and yogurt samples (McNeal and Breder 1987).

7.2 ENVIRONMENTAL SAMPLES

Standardized methods for determining 1,3-butadiene in environmental samples are limited to air samples, as no methodology has been described for analyzing this compound in water or soil samples (EPA 1982, 1986). A representative list of the methods available for the determination of 1,3-butadiene in air samples can be found in Table 7-1. The determination of 1,3-butadiene in personal air can be obtained using the procedures outlined in NIOSH Method 1024 (NIOSH 1994) and OSHA Method 56 (OSHA 2009a) or EPA Methods TO-14A and TO-15 (EPA 1999a, 1999b).

For NIOSH Method 1024, the air sample is obtained by passing a known volume of air (5–25 L) through a set of tandem coconut charcoal tubes, which adsorb 1,3-butadiene and remove it from the air stream (NIOSH 1994). The collected 1,3-butadiene is then removed from the adsorption tube by extraction with methylene chloride. Injection of the methylene chloride solution into a GC equipped with a flame ionization detector (FID) separates 1,3-butadiene from any interfering compounds that may be present. The choice of chromatography column for this determination is not crucial, as long as it cleanly separates 1,3-butadiene from other compounds.

The estimated quantitation limit (LOQ) of this method is 0.02 ppm, with an applicable range of 0.04–220 µg per sample (approximately 0.04–100 ppm) for a 25 L sample. The precision of this method appears to change as a function of the concentration being measured, due to desorption efficiencies changing as a function of sample concentration. With increasing concentration, the preparation of a standard becomes more difficult. A limitation of this study is the relatively high LOQ (20 ppb), since concentrations observed in environmental settings are often <1 ppb.

In NIOSH Method 1024, quantitation of 1,3-butadiene is accomplished by comparing the area under the sample's response signal to that of a known amount of 1,3-butadiene. The preparation and injection of a gaseous 1,3-butadiene standard is a difficult procedure; it must be performed carefully or erroneous results will occur. Sample storage appears to dramatically affect the results of the measurement. Samples stored at -4 °C displayed an average recovery of 93–98% over a 21-day period, while samples stored at room temperature ranged from 61 to 95%.

OSHA Method 56 for analyzing 1,3-butadiene in air samples is similar to the NIOSH method described above. Air is drawn through sampling tubes containing charcoal absorbent coated with 4-*tert*-butyl-catechol. The samples are then desorbed with carbon disulfide and analyzed using gas chromatograph-

Table 7-1. Analytical Methods For Determining 1,3-Butadiene in Environmental Samples

Sample air	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Personal air (Method 1024)	Pass air through charcoal tube followed by desorption with methylene chloride	GC/FID	0.04–220 µg/sample (25L sample)	61–98	NIOSH 1994
Personal air (Method 56)	Pass air through charcoal tube coated with 4-*tert*-butylcatechol followed by desorption with carbon disulfide	GC/FID	200 µg/m^3 (90 ppb)	77–94	OSHA 2009a
Air (Method TO-14A)	Pressurized container sampling followed by cryogenic concentration	GC/MS/SIM or SCAN	No data	No data	EPA 1999a
Air (Method TO-15)	Pressurized container sampling followed by multisorbent concentration and thermal desorption	GC/MS/SIM or SCAN	No data	No data	EPA 1999b
Air	Collect air in Tedlar bag concentrate on Tenax cartridge, thermal desorption	GC/FID	No data	No data	Stump and Dropkin 1985
Air	Pass air through charcoal tube solvent desorption	GC/MS	No data	No data	Texax Air Control Board 1990
Air (real time)	Draw air into 12-foot sampling loop, direct injection	GS/MS	No data	No data	Texax Air Control Board 1990
Air	Pass air through sorbent tubes containing Carbopack B/Carbosieve SIII followed by thermal desorption	GC/MS	0.11–0.16 µg/m^3	>95%	Kim et al. 1999

FID = flame ionization detector; GC = gas chromatography; MS = mass spectrometry; SCAN = wide range of mass to charge ratio scanning; SIM = select ion monitoring

flame ionization detector (GC-FID). The recommended air volume and sampling rate is 3 L at 0.05 L/minute. The detection limit is 200 μg/m^3 and the quantitation limit is 343 μg/m^3. As with NIOSH Method 1024, the usefulness of OSHA Method 56 for analysis of 1,3-butadiene in environmental media is limited since the reported detection and quantitation limits are much higher than levels often observed in environmental settings.

1,3-Butadiene, along with other volatile hydrocarbons, has been found in ambient air samples by a technique that uses cryogenic concentration before GC analysis. This technique is performed by collecting a large volume of air in a specially designed bag or other sampling container and concentrating the volatile components by condensation at low temperatures. The sample is separated into its components by GC and quantified with an internal standard. Numerous variations of this method were found in the literature (Curren 2006; Graham et al. 2004; Lonneman et al. 1979; Neligan 1962; Stephens and Burleson 1967, 1969; Stump and Dropkin 1985).

EPA Methods TO-14A and TO-15 describe procedures for the analysis of volatile organic compounds (VOCs) in air (EPA 1999a, 1999b). Method TO-14A calls for cryogenic concentration of the air sample as described above. Method TO-15 calls for pressurized air sampling using a stainless steel canister. The sample is then passed through a solid multisorbent concentrator and the concentrator is finally dry-purged with helium. The sample is thermally desorbed prior to analysis. For both of these methods, analysis is performed using GC followed by either a specific or nonspecific detector. However, the use of a specific detector is recommended, such as linear quadrupole mass spectrometer operating in either select ion monitoring (SIM) mode or a mode that scans a wide range of mass to charge ratios (SCAN). Precision and recovery data for 1,3-butadiene are not specified in these methods. Kim et al. (1999) developed an improved method by using a combination Carbopack B/CarbosieveSIII sorbent as a collection material. Sample collection was followed by thermal desorption and GC/MS analysis. These authors reported a precision of 2.4–13%, recoveries of >95%, and a detection limit of 0.11–0.16 μg/m^3 for this method. Therefore, this method is useful for measuring 1,3-butadiene concentrations in the low ppb (μg/m^3) range in environmental air samples.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-butadiene is available. Where adequate information is

not available, ATSDR, in conjunction with NTP is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-butadiene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No standardized method for the determination of biomarkers of exposure and effect for 1,3-butadiene was located.

Exposure. Biomarkers that have been proposed as indicators of exposure to 1,3-butadiene include the urinary metabolites 1,2-dihydroxybutyl mercapturic acid (DHBMA or M1) and 1- and 2-monohydroxy-3-butenyl mercapturic acid (MHBMA or M2) and the hemoglobin adducts 1- and 2-hydroxy-3-butenyl valine (MHB-Val) and N-(2,3,4-trihydroxy-butyl)valine (THB-Val) (Albertini et al. 2001; Boogaard et al. 2001a; Carrieri et al. 2009; McDonald et al. 2004; Sapkota et al. 2006; Schettgen et al. 2009; Shen et al. 2009). Measurement of unmetabolized 1,3-butadiene in human blood and urine may be preferable for assessing very low levels of exposure to this substance (0.4 μg/m^3 median concentration in personal air) (Fustinoni et al. 2004; Perbellini et al. 2003; Schettgen et al. 2009).

Both the urinary metabolites and the hemoglobin adducts have been well correlated with exposure to 1,3-butadiene (Albertini et al. 2001; Preston 2007). Methods developed to measure these biomarkers have utilized either HPLC or GC followed by tandem MS (Boogaard et al. 2001a; Carrieri et al. 2009; Sapkota et al. 2006; Schettgen et al. 2009). Shen et al. (2009) has developed a method based on liquid chromatography/electrospray ionization-mass spectrometry to measure 3-butene-1,2-diol, a 1,3-butadiene urinary metabolite intermediate.

Effect. Biomarkers of effect resulting from 1,3-butadiene exposure, such as gene mutation and chromosomal changes, have been explored; however, no clear associations have been observed (Albertini et al. 2001; Preston 2007).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Data on the determination of 1,3-butadiene in environmental media were limited. 1,3-Butadiene in air samples has been detected by techniques routinely used for detecting volatile hydrocarbons (Kim et al. 1999; Stump and Dropkin 1985; Texas Air Control Board 1990; EPA 1999a, 1999b). Improvements to these methods have made possible the detection of 1,3 butadiene concentrations in the low ppb ($\mu g/m^3$) range in environmental air samples (Kim et al. 1999). Procedures accepted for the determination of volatile hydrocarbons in other environmental media (soil, water, sediment, plants, etc.) may also be suitable for 1,3-butadiene. This question can be answered only by the data obtained from properly designed experiments. The information will assist in determining the prevalence of this compound in the environment and aid in a quantitative determination of human exposure to 1,3-butadiene.

7.3.2 Ongoing Studies

Ongoing studies related to the development of analytical methods for 1,3-butadiene were not located.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

EPA (IRIS 2012) has established an inhalation reference concentration (RfC) for 1,3-butadiene of 0.9 ppb based on a $BMCL_{10}$ of 0.88 ppm for ovarian atrophy in female B6C3F1 mice exposed to 1,3-butadiene by inhalation for 6 hours/day, 5 days/week for up to 103 weeks.

EPA has not established an oral reference dose (RfD) for 1,3-butadiene (IRIS 2012).

OSHA has required employers of workers who are occupationally exposed to 1,3-butadiene to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2009b). The employer must use engineering and work practice controls to reduce exposures to not exceed 1 ppm for 1,3-butadiene at any time (OSHA 2009b).

EPA has designated 1,3-butadiene as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) (EPA 2009b). 1,3-Butadiene is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 100 pounds (EPA 2009d). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

The international and national regulations, advisories, and guidelines regarding 1,3-butadiene in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1,3-Butadiene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 1[a]	IARC 2009
WHO	Air quality guidelines	No guideline value is recommended at this time	WHO 2000
	Drinking water quality guidelines	No	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	2 ppm	ACGIH 2008
AIHA	ERPG-1[b]	10 ppm	AIHA 2008
	ERPG-2[b]	200 ppm	
	ERPG-3[b]	5,000 ppm	
EPA	RfC	0.9 ppb	IRIS 2012
	Inhalation unit risk	3×10^{-5} per $\mu g/m^3$	
EPA	AEGL-1[c]		EPA 2009a
	10 minutes	670 ppm	
	30 minutes	670 ppm	
	60 minutes	670 ppm	
	4 hours	670 ppm	
	8 hours	670 ppm	
	AEGL-2[c]		
	10 minutes	6,700 ppm	
	30 minutes	6,700 ppm	
	60 minutes	5,300 ppm	
	4 hours	3,400 ppm	
	8 hours	2,700 ppm	
	AEGL-3[c]		
	10 minutes	27,000 ppm	
	30 minutes	27,000 ppm	
	60 minutes	22,000 ppm	
	4 hours	14,000 ppm	
	8 hours	6,800 ppm	
	Level of distinct odor awareness	3.7 ppm	
	Hazardous air pollutant	Yes	EPA 2009b 42 USC 7412

Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1,3-Butadiene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Regulated flammable substances and threshold quantities for accidental release prevention[d]	10,000 pounds	EPA 2009c 40 CFR 68.130
NIOSH	REL (10-hour TWA)	Potential occupational carcinogens	NIOSH 2005
	IDLH (10% LEL)	2,000 ppm	
	Target organs	Eyes, respiratory system, central nervous system, and reproductive system	
OSHA	PEL (8-hour TWA) for general industry	1 ppm	OSHA 2009b 29 CFR 1910.1051
	STEL (15-minutes)	5 ppm	
b. Water			
EPA	Drinking water standards and health advisories	No	EPA 2006a
	National primary drinking water standards	No	EPA 2003b
	National recommended water quality criteria	No	EPA 2006b
c. Food			
FDA	EAFUS[e]	No	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification	A2[f]	ACGIH 2008

Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1,3-Butadiene

Agency	Description	Information	Reference
EPA	Carcinogenicity classification	Carcinogenic to humans by inhalation	IRIS 2012
	RfD	No data	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes[g]	EPA 2009d 40 CFR 302.4
	Reportable quantity	100 pounds	
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2009e 40 CFR 372.65
NTP	Carcinogenicity classification	Known to be a human carcinogen	NTP 2005

[a]Group 1: carcinogenic to humans
[b]ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing other than mild, transient health effects; ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing irreversible or other serious adverse effects; and ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without life-threatening health effects (AIHA 2008).
[c]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects, however, the effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; and AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2009a).
[d]Basis for listing: flammable gas
[e]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[f]A2: suspected human carcinogen
[g]Designated CERCLA hazardous substance pursuant to Section 112 of the Clean Air Act

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; LEL = lower explosive limit; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

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

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

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

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

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences (proposed), expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences (proposed), Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

SAMPLE

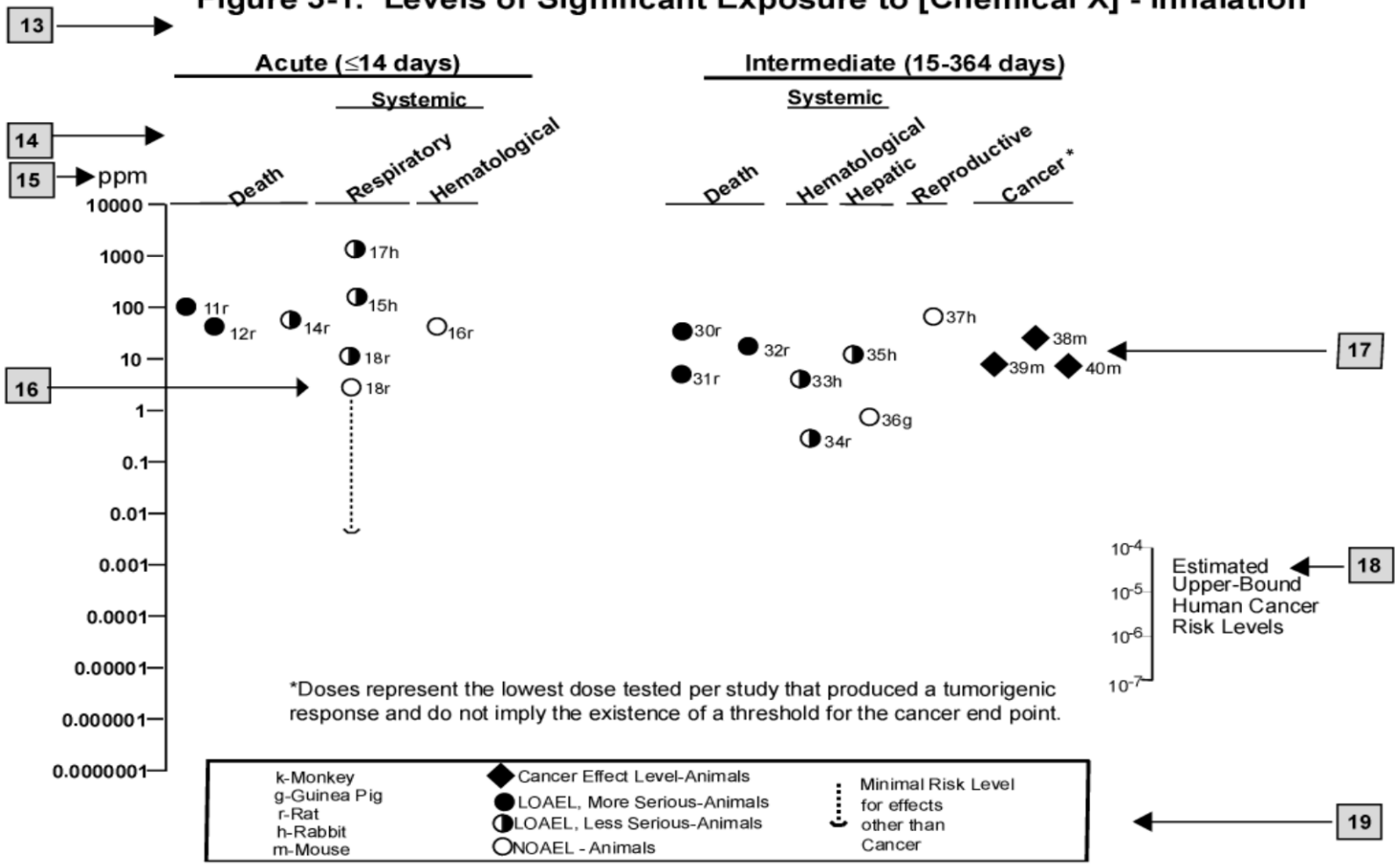
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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

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APPENDIX D. INDEX