

Overview information for

1,3-Butadiene

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

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

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:

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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.



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Agency for Toxic Substances and Disease Registry

*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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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. PUBLIC HEALTH STATEMENT

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

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| Sources | <p>Large amounts of 1,3-butadiene are released into the air by industrial sources. Industrial releases to water and soil are relatively low.</p> <p>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.</p> <p>Forest fires are considered to be a natural source of 1,3-butadiene in the air.</p> |
| Break-down <ul style="list-style-type: none">• Air• Water and soil | <p>Half of the 1,3-butadiene in the air will likely be broken down in about 6 hours.</p> <p>1,3-Butadiene that is spilled onto water or soil will likely evaporate quickly into the air based on its physical and chemical properties.</p> |

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?

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| Air | <p>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:</p> <ul style="list-style-type: none">• vehicle exhaust• tobacco smoke• wood burning• burning of rubber and plastic• forest fires• accidental or intentional release at manufacturing plants <p>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.</p> |
| Workplace air | <p>Workers in the production of rubber, plastics, and resins are likely exposed to higher levels of 1,3-butadiene.</p> |

1. PUBLIC HEALTH STATEMENT

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| 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?

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|------------------------|--|
| 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.

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

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| Cancer | <p>Studies of workers exposed to 1,3-butadiene suggest that workers may have an increased risk for cancers of the blood and lymphatic system.</p> <p>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.</p> <p>The International Agency for Research on Cancer (IARC), National Toxicology Program (NTP), and EPA all classify 1,3-butadiene as a human carcinogen.</p> |
|---------------|---|

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.

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| 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?

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| 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. PUBLIC HEALTH STATEMENT

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. PUBLIC HEALTH STATEMENT

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/>

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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 $\mu\text{g}/\text{m}^3$ (0.04–1 ppb); the average background concentration of 0.13 $\mu\text{g}/\text{m}^3$ (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 $\mu\text{g}/\text{m}^3$ (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-dihydroxy-1,4-butadiyl)valine (*pyr*-Val), which are surrogate biomarkers for the 1,3-butadiene metabolites 1,2 epoxy-3-butene (EB),

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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

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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 $\geq 19\%$ 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

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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-hematopoietic 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).

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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 Elfarrar 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 hemoglobin 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,

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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 $\geq 1,000$ 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

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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

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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

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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 BMCL₁₀ 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 BMCL₁₀ for intermittent exposure (6 hours/day, 5 days/week) and multiplying the adjusted BMCL₁₀ 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 BMCL₀₅ 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-

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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 <i>pyr</i> -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

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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 BMCL₀₁ 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.

2. RELEVANCE TO PUBLIC HEALTH

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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

3. HEALTH EFFECTS

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 $\leq 8,000$ 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

3. HEALTH EFFECTS

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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|--------|----------------|---|--|----------------------------|----------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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 | | Reference Chemical Form | Comments |
|-------------------------------|-------------------------|--|--------|----------------|-------------------------------------|---|----------------------------|----------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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) | | Irvine 1981 | |
| | | | | | 1000 (major skeletal malformations) | | | |
| 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|-----------|----------------|-----------------------|--|---------------------------------------|----------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|-----------|----------------|--|------------------|----------------------------|----------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|-----------|----------------|--|---|----------------------------|----------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|--------|----------------|--|--|----------------------------|----------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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/adenocarcinoma, 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|---------|----------------|--|----------------------------|---|----------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|-----------|----------------|-----------------------|---|----------------------------|--|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 31 | Mouse | 61 wk 5 d/wk 6 hr/d | Resp | 625 | | 1250 | NTP 1984 | (atrophy of nasal olfactory epithelium) |
| | | | 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|--------|----------------|-----------------------|--|---|---------------------------------|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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 | | Reference Chemical Form | Comments |
|-------------------------------|---------------------|--|--------|----------------|-----------------------|------------------|---|--|
| | | | | | Less Serious (ppm) | Serious (ppm) | | |
| 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)

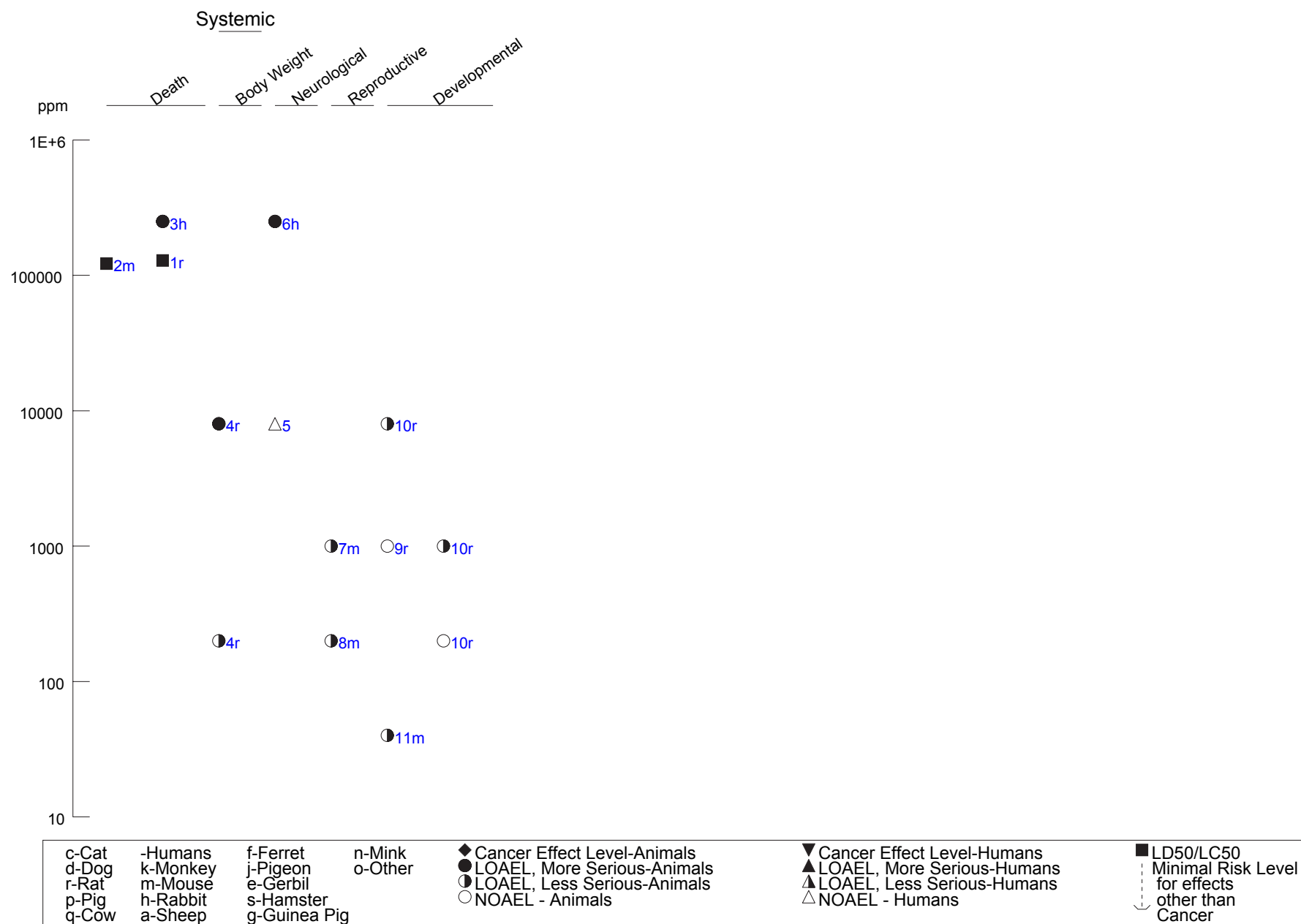


Figure 3-1 Levels of Significant Exposure to 1,3-Butadiene - Inhalation (Continued)

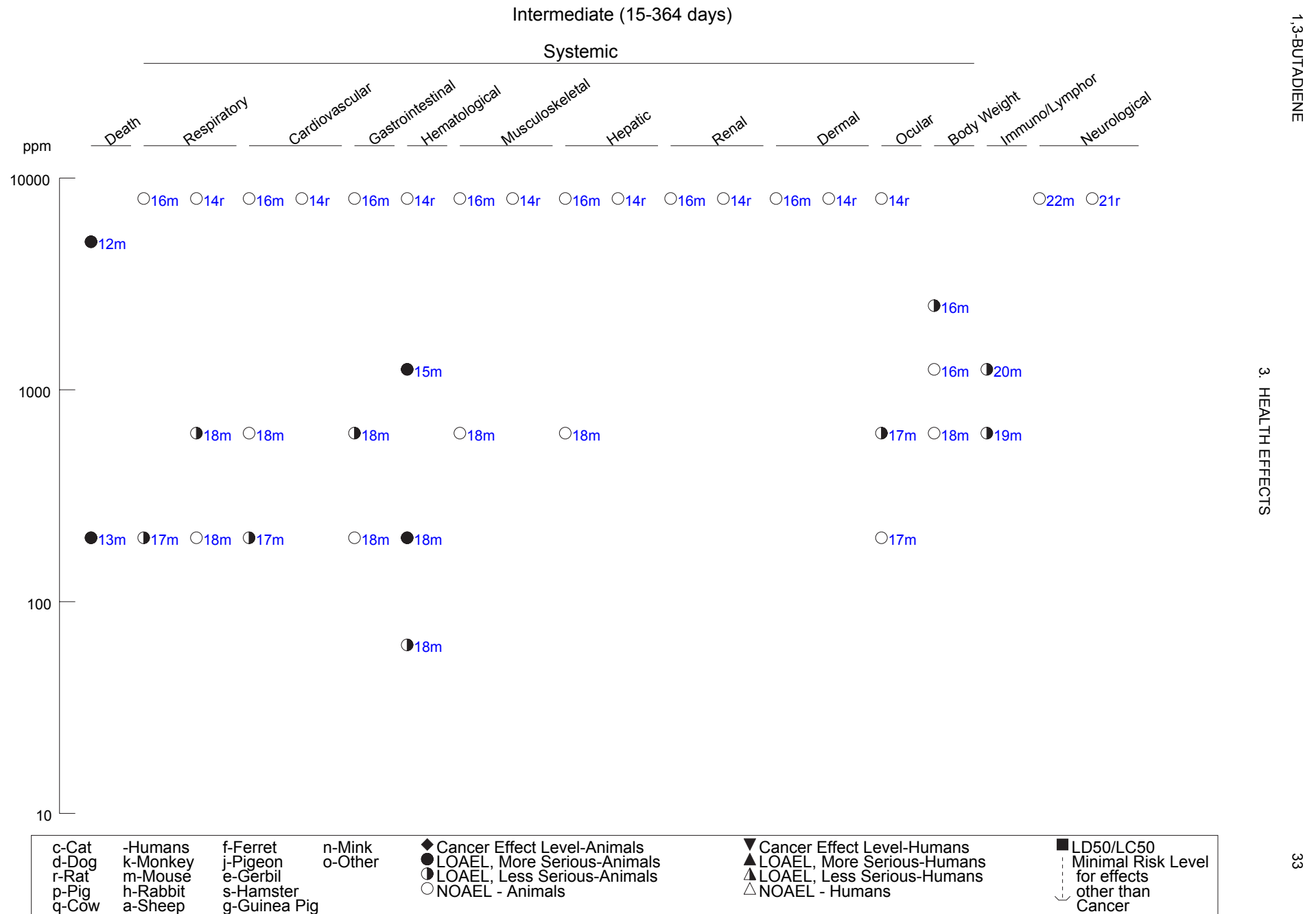
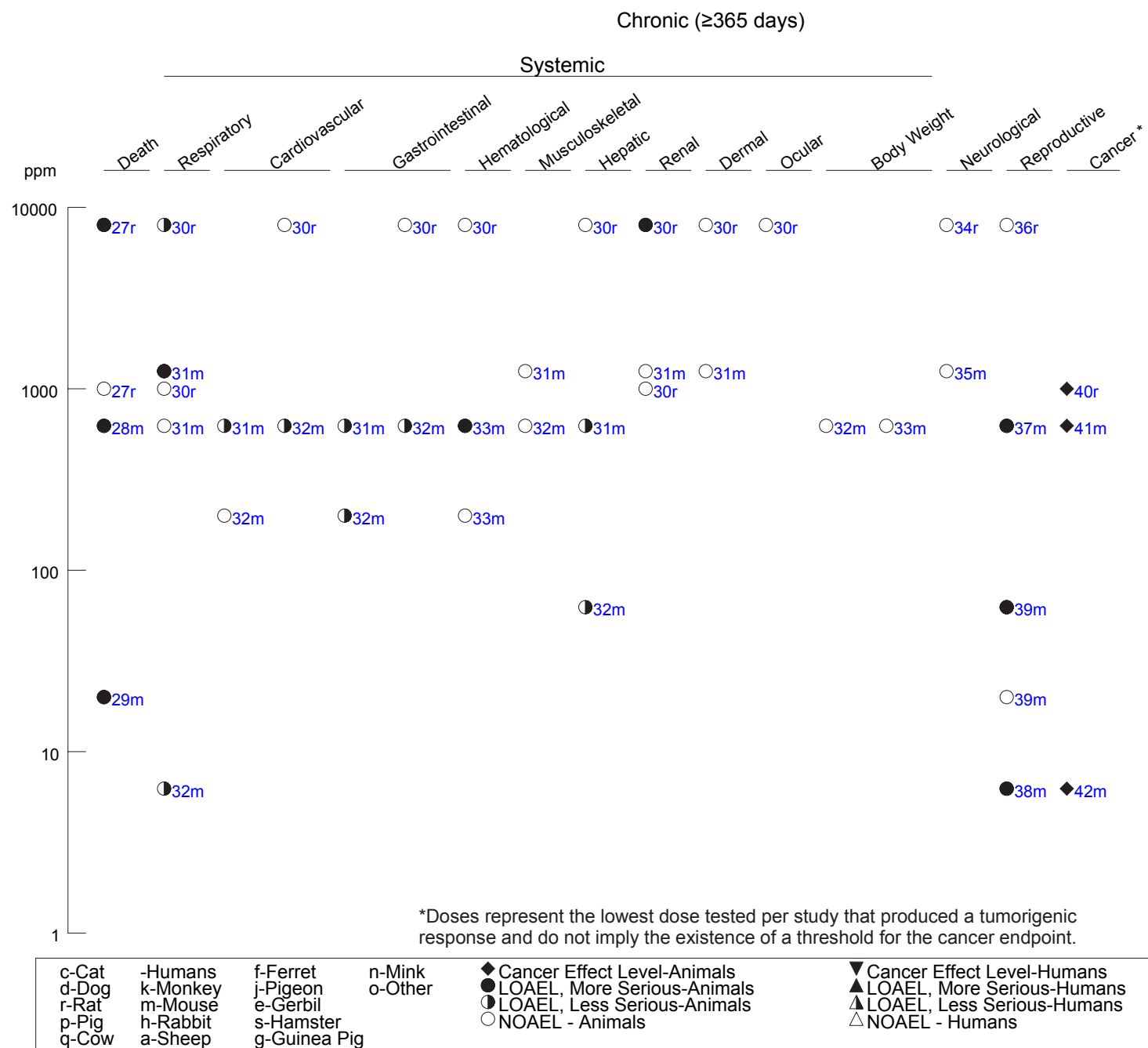


Figure 3-1 Levels of Significant Exposure to 1,3-Butadiene - Inhalation (*Continued*)

Intermediate (15-364 days)



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



3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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).

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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).

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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

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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

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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 $\leq 6,700$ 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.

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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

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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 dimethyldithiocarbamate, 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

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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

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(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,

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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 hemangiosarcoma, 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 hemangiosarcoma, 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 1×10^{-3} – 1×10^{-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.

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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-butadiene 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 hypoxanthine-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

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

| Species (test system) | End point | Results | | Reference |
|--------------------------------|--|-----------------|--------------------|---|
| | | With activation | Without activation | |
| Prokaryotic organisms: | | | | |
| <i>Salmonella typhimurium</i> | | | | |
| 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 | <i>hprt</i> and <i>tk</i> loci mutations | NA | NA | Cochrane and Skopek 1993 |

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

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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) | <i>lacZ</i> ⁻ mutant frequency in lung | + | Recio et al. 1992 |
| B6C3F1 mice (inhalation) | <i>lacZ</i> ⁻ mutant frequency in liver and bone marrow | - | Recio et al. 1992 |
| B6C3F1 mice and F344 rats (inhalation) | <i>hprt</i> 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 Tate 1995 |
| CD-1 mice (inhalation) | Dominant lethality | - | Brinkworth et al. 1998 |
| CAST/EiJ, NOD/LTj, A/J, WSB/EiJ, PWK/PhJ, 129S/SvImJ, 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) | <i>hprt</i> loci in peripheral lymphocytes | - | Hayes et al. 1996, 2000 |
| Humans (inhalation) | <i>hprt</i> loci in peripheral lymphocytes | - | Tates et al. 1996 |
| Humans (inhalation) | <i>hprt</i> loci in peripheral lymphocytes | - | Albertini et al. 2001, 2007; HEI 2003 |

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

| Species (test system) | End point | Results | Reference |
|--------------------------|--|---------|--|
| Humans (inhalation) | <i>hprt</i> loci in peripheral lymphocytes | - | Liu et al. 2008 |
| | <i>hprt</i> exon deletion | + | Liu et al. 2008 |
| Humans (inhalation) | <i>hprt</i> loci in peripheral lymphocytes | + | Ward et al. 1994 |
| Humans (inhalation) | <i>hprt</i> loci in peripheral lymphocytes | + | Abdel-Rahman et al. 2001, 2003, 2005; Ma et al. 2000; Ward et al. 1996, 2001 |
| Humans (inhalation) | <i>hprt</i> 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- <i>ras</i> 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

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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

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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

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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/m³ [0.29 ppm]) and 34 workers at a polymerization facility (mean exposure level of 1.76 mg/m³ [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/m³ (0.18 ppm) and 0.808 mg/m³ (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/m³ [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; Tate 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*

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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 Tate 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 F₁ 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

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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.

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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 $\mu\text{mol}/\text{hour}/10\text{ ppm}$ of inhaled and 3.20 $\mu\text{mol}/\text{hour}/10\text{ ppm}$ 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

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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 ¹⁴C-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.

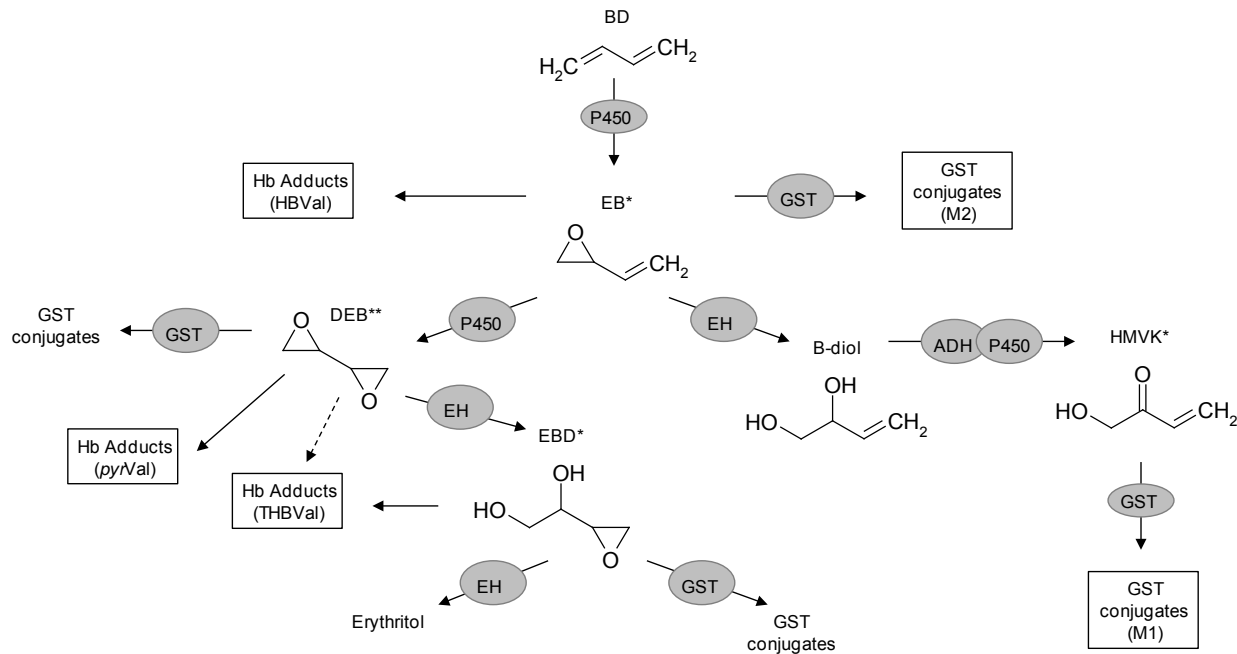
3.4.2.3 Dermal Exposure

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

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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;

pyrVal = *N,N*-(2,3-dihydroxy-1,4-butadiyl)-valine; THBVal = *N*-(2,3,4-trihydroxybutyl)-valine

Source: Kirman et al. 2010

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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 (Elfarrar 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 Elfarrar 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 hydrolyzed via epoxide hydrolase (EH) to 3-butene-1,2-diol (BDdiol). BDdiol is metabolized via CYP or aldehyde dehydrogenase (ADH) to the ketone 1-hydroxy-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) (Elfarrar 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 (Elfarrar 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

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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 al. 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-butadiene 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,

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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

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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 depletion and saturable kinetics have been proposed as possible sources of nonlinear kinetics. Studies evaluating effects of hepatic glutathione levels show that glutathione 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-dihydroxybutyl)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.

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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 $\leq 1,000$ 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 $\mu\text{mol}/\text{hour}/\text{kg}$ for rats (Laib et al. 1988) and 400 $\mu\text{mol}/\text{hour}/\text{kg}$ 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.

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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 (Clewett 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

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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.

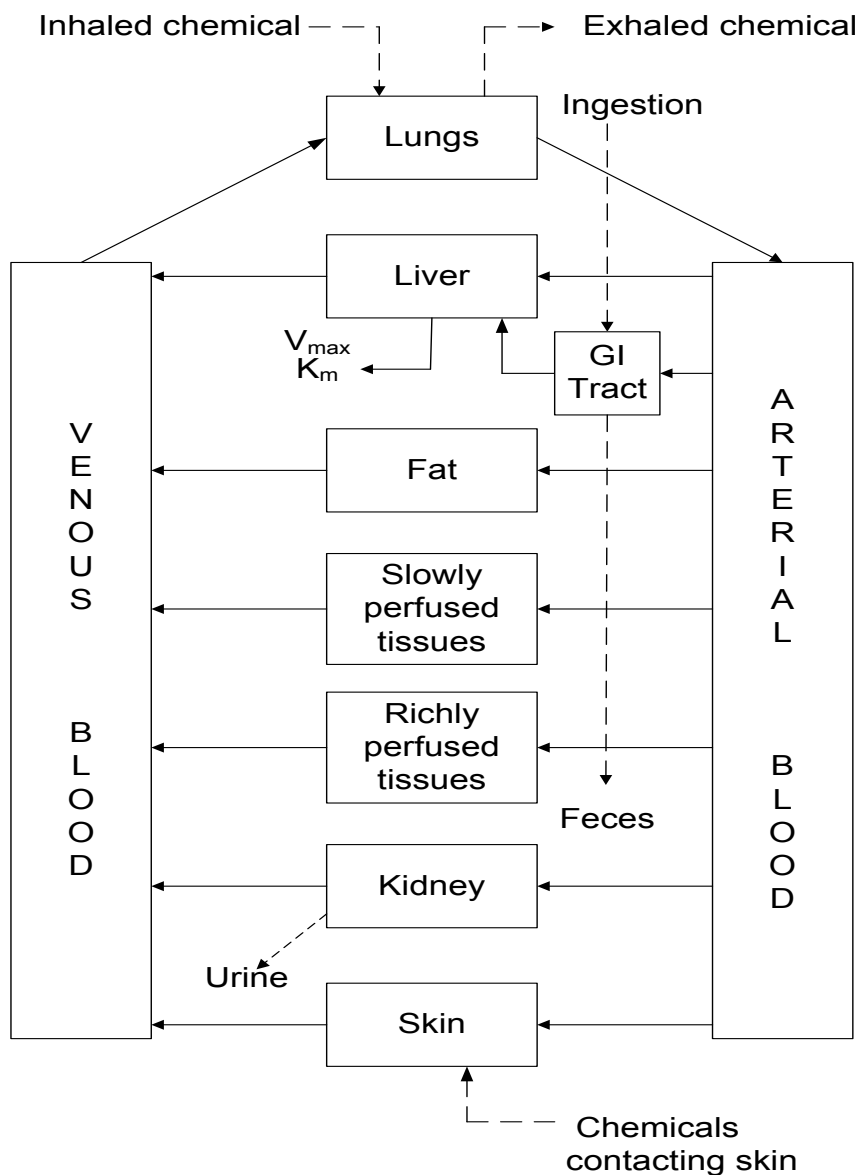
Literature on PBPK modeling of 1,3-butadiene is extensive (Beaudouin et al. 2010; Bois et al. 1999; Bond et al. 1996; Brochot et al. 2007; Csanady et al. 1996; Evelo et al. 1993; Filser et al. 1993; Johanson and Filser 1993, 1996; Kohn 1997; Kohn and Melnick 1993, 1996, 2000, 2001; Leavens and Bond 1996, 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.

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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

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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.

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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 |
| | Lung and arterial | | 1 | 1 |
| Compartment volumes ^a (percent of body weight) | 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 |

^aDensity 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)

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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.

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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

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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

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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, <i>67.1</i> | 1.0, <i>31.5</i> | 1.0, 85.0 |
| K_m^{P450} | 0.0156, 0.145 | 0.0156, 0.145 | 0.0156, 0.145 |
| V_{\max}^{GST} | 3,480, <i>1,230</i> | 491, <i>276</i> | 1,070, 658 |
| K_{mx}^{GST} | 34, 34 | 34, 34 | 34, 34 |
| Epoxybutanediol metabolism | | | |
| V_{\max}^{EH} | 363, <i>1,150</i> | 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, <i>100</i> | 100, <i>100</i> |
| 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 |
| $V_{\max}^{\gamma-GCS}$ | 420, 396 | 54, 50 | 7,920, 6,080 |

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

^aNon-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

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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-diepoxibutane, 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.

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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 1,2:3,4-diepoxibutane 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 1st-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 vicinal 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.

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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 |

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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 |

^aMean 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

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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 vicinal 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 nonenzymatic 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.

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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 |

^aAlveolar 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.

^bTissue blood flows are calculated by multiplying the total cardiac output by the fractional flow: $Q_i = F_i \times Q_t$.

^cTissue volumes are calculated by multiplying the body weight by the fractional volume: $V_i = F_i \times BW$.

Source: Sweeney et al. 1997

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

| Tissue | Butadiene ^a | | Epoxybutene ^a | | Diepoxybutane ^b |
|--------|------------------------|-------|--------------------------|-------|----------------------------|
| | 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 |

^aTissue:air partition coefficients.^bTissue:hexane partition coefficient.

ND = not determined

Source: Sweeney et al. 1997

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

| Tissue | Epoxybutene | | Diepoxybutane | |
|--------|-------------|-------|---------------|-------|
| | 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

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

| Substrate | Tissue | Pathway | Units | Parameter value | |
|---------------|--------|-------------------------|--------------|-----------------|---------|
| | | | | 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 |
| | | Glutathione conjugation | μmol/kg/hour | 819 | 4,088 |
| Diepoxybutane | Liver | | μmol/L | 17,400 | 36,500 |
| | | 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

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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 | $QP = QPC \times BW$ |
| Cardiac output (QCC) | 4.5 | L/hour/kg body weight | $QC = QCC \times BW$ |
| Fractional blood flow to liver | 0.227 | Dimensionless | $QR = 0.76 \times QC - QL$ |
| Fractional blood flow to fat | 0.052 | Dimensionless | $QS = 0.24 \times QC - QF$ |
| 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

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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

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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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ 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 ($\mu\text{mol}/\text{mg}$ cytosolic protein/hour) | 0.2 |
| K_m for conjugation of epoxybutane diol and glutathione (μM) | 3,390 |

^aMedian or average parameter values.

Source: Sweeney et al. 2001

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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

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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,

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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

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genotoxicity of 1,3-butadiene metabolites (Cunninham et al. 1986; Jauhar et al. 1988; Lovreglio et al. 2006; Sharief et al. 1986; Sram et al. 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 ED₅₀ (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 $\leq 8,000$ 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

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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-

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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 isoflavonoid 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).

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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

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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).

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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

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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-butadiene 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

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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 (N7-(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

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(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), hemangiosarcomas (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;

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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 be 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

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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 CYP2E1 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

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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

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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

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

| | Systemic | | | | | | | | | |
|------------|----------|-------|--------------|---------|-------------------------|------------|--------------|---------------|-----------|--------|
| | Death | Acute | Intermediate | Chronic | Immunologic/Lymphoretic | Neurologic | Reproductive | Developmental | Genotoxic | Cancer |
| Inhalation | ● | | ● | | ● | | | ● | ● | |
| Oral | | | | | | | | | | |
| Dermal | | | | | | | | | | |

Human

| | Systemic | | | | | | | | | |
|------------|----------|-------|--------------|---------|-------------------------|------------|--------------|---------------|-----------|--------|
| | Death | Acute | Intermediate | Chronic | Immunologic/Lymphoretic | Neurologic | Reproductive | Developmental | Genotoxic | Cancer |
| Inhalation | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Oral | | | | | | | | | | |
| Dermal | | | | | | | | | | |

Animal

● Existing Studies

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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

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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 $\geq 1,000$ 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

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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.

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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

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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), hemangiosarcomas (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.

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Absorption, Distribution, Metabolism, and Excretion. The timecourse 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.

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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,

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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 lymphohematopoietic (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

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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

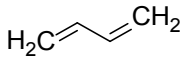
4.1 CHEMICAL IDENTITY

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 ₄ H 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 |

^aAll information obtained from HSDB 2009 and ChemID Plus Advanced 2009 except where noted.

^bO'Neil et al. 2006.

^cNIOSH 2005.

^dMiller 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 |

^aAmoore 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.

^bThis K_{oc} value was estimated using the measured log K_{ow} value (1.99) and a regression derived equation.

^cThis Henry's Law constant value was calculated from the measured vapor pressure (2.11x10³ 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

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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

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

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 |

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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 |

^aPost office state abbreviations used.^bAmounts on site reported by facilities in each state.^cActivities/Uses:

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

Source: TRI09 2011 (Data are from 2009)

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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

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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).

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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).

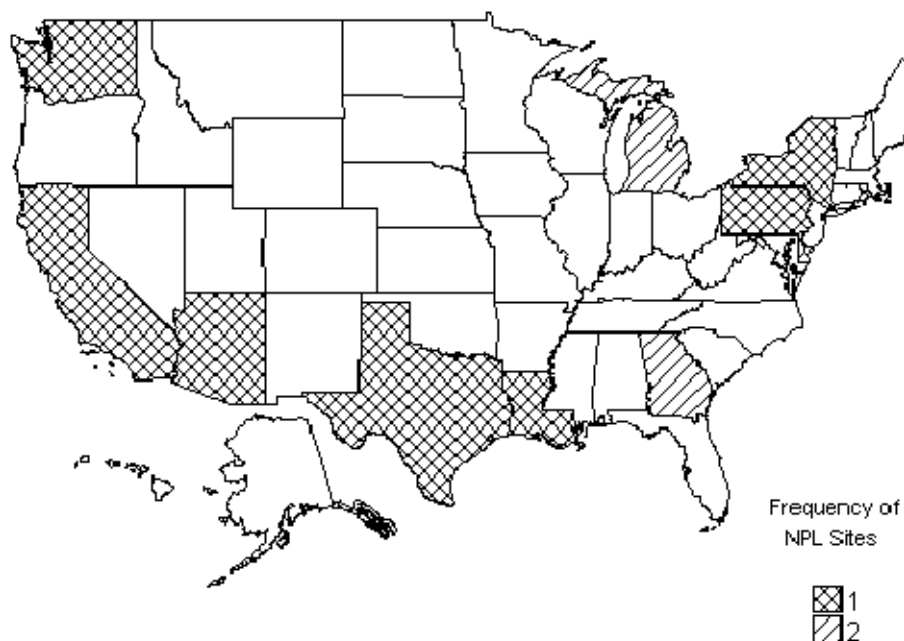
1,3-Butadiene may be released to the environment as an intentional or fugitive emission during its production, use, storage, transport, or disposal. Large amounts (1.17 million pounds) of this hydrocarbon are released to the atmosphere from commercial processes (TRI09 2011). Data on the detection of 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.

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

Derived from HazDat 2007

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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,

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imports, or processes $\geq 25,000$ 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 $\mu\text{g}/\text{cigarette}$ (Brunnemann et al. 1990), with an average airborne yield of 400 $\mu\text{g}/\text{cigarette}$ (Lofroth et al. 1989).

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

| State ^c | RF ^d | Reported amounts released in pounds per year ^b | | | | | | | |
|--------------------|-----------------|---|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
| | | Air ^e | Water ^f | UI ^g | Land ^h | Other ⁱ | Total release | | |
| | | | | | | | 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 |

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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 | | | | | | | | | |
|---|-----------------|------------------|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
| State ^c | RF ^d | Air ^e | Water ^f | UI ^g | Land ^h | Other ⁱ | Total release | | |
| | | | | | | | 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 |

^aThe 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.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI09 2011 (Data are from 2009)

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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 |

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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 |

^aEmission 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

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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

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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 7.4×10^{-2} atm-m³/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

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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 $6.85 \times 10^{-11} \text{ cm}^3/\text{molecule-second}$ at 26 °C (Atkinson et al. 1977) is representative. Given an average hydroxyl radical concentration of $5 \times 10^5 \text{ molecule/cm}^3$ (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).

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Gas-phase 1,3-butadiene also reacts with ozone in the atmosphere. Rate constants ranging from 6.7×10^{-18} to 8.4×10^{-18} cm³/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 7×10^{11} molecules/cm³ (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 5.4×10^{-14} cm³/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 2.4×10^8 molecule/cm³ (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-epoxybutene (Hou et al. 1979, 1980, 1983; Patel et al. 1982a; Watkinson and Somerville 1976). Watkinson and Somerville (1976) reported further degradation.

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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 $\mu\text{g}/\text{m}^3$ (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 $\mu\text{g}/\text{m}^3$ (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 $\mu\text{g}/\text{m}^3$ (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 $\mu\text{g}/\text{m}^3$ (0.058 ppb). McCarthy et al. (2006)

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provided a lower estimate ($<0.02 \mu\text{g}/\text{m}^3$; 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 $1.0 \mu\text{g}/\text{m}^3$ (0.5 ppb) during the winter and $1.2 \mu\text{g}/\text{m}^3$ (0.54 ppb) during the summer (Sax et al. 2004). In Los Angeles, mean concentrations were $0.5 \mu\text{g}/\text{m}^3$ (0.2 ppb) during the winter and $0.2 \mu\text{g}/\text{m}^3$ (0.09 ppb) during the fall. The concentrations of 1,3-butadiene measured in a tavern were 11 and $19 \mu\text{g}/\text{m}^3$ (5.0 and 8.6 ppb) in two separate studies, while the outside air concentration was $\leq 1 \mu\text{g}/\text{m}^3$ (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 $2.7\text{--}4.5 \mu\text{g}/\text{m}^3$ (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 $0.5 \mu\text{g}/\text{m}^3$ (0.77 and 0.23 ppb), respectively (Kim et al. 2001). Mean 1,3-butadiene levels were 0.31–0.38 $\mu\text{g}/\text{m}^3$ (0.14–0.17 ppb) in the air of wood burning homes and $0.114 \mu\text{g}/\text{m}^3$ (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, Contra Costa, 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.

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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 |

^aValue is referred to as the reporting limit.^bLower and upper median values correspond to measurements taken during 12–3 a.m. and 6–9 a.m., respectively.^cSeven-hour samples were collected on 18 week days and 6 weekend days.^dLower and upper median values correspond to measurements taken on weekends and weekdays, respectively.

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

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

| Location | Concentration ($\mu\text{g}/\text{m}^3$) | | | | | | 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 | — | |

^aConcentrations measured in the house and garage after a cold vehicle engine was started in the attached garage.

^bIncludes offices, department stores, cinemas, perfume shop, libraries, and laboratories.

^c90th percentile values.

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

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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/m³ (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/m³ (0.55 ppb) for suburban-weekend exposure, 1.47 µg/m³ (0.66 ppb) for urban-week day exposure, and 2.88 µg/m³ (1.3 ppb) for tollbooth worker exposure in the Baltimore, Maryland area.

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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 $\mu\text{g}/\text{cigarette}$ (Pankow et al. 2004; Thweatt et al. 2007). Nazaroff and Singer (2004) calculated a 1,3-butadiene inhalation intake of 16–37 $\mu\text{g}/\text{day}$ 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 $\mu\text{g}/\text{m}^3$ (Nazaroff and Singer 2004). Counts et al. (2006) measured 1,3-butadiene concentrations ranging from 11.2 to 59.3 $\mu\text{g}/\text{cigarette}$ 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 $\mu\text{g}/\text{m}^3$ (0.15 ppb) in the personal air of individuals living in wood-burning homes and 0.14 $\mu\text{g}/\text{m}^3$ (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 $\mu\text{g}/\text{m}^3$), 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 $\mu\text{g}/\text{day}$ based on an exposure concentration of 0.55 $\mu\text{g}/\text{m}^3$ and a mean breathing rate of 13.1 m^3/day . Kim et al. (2002) measured mean personal air exposure concentrations of 1.1 $\mu\text{g}/\text{m}^3$ (0.50 ppb) during the night time and 0.8 $\mu\text{g}/\text{m}^3$ (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

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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/m³; 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/m³ (673 ppm).

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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 |

^aAir samples were collected at different times at a Canadian synthetic rubber plant between 1977 and 1991.

Source: Sathiakumar et al. 2007

6. POTENTIAL FOR HUMAN EXPOSURE

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 $<0.006 \text{ ppm}$ to 374 ppm ($0.013\text{--}827 \text{ mg/m}^3$) (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 $11.5 \text{ } \mu\text{g/m}^3$ (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 $0.9 \text{ } \mu\text{g/m}^3$ (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.

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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

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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

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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

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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*-butylcatechol. The samples are then desorbed with carbon disulfide and analyzed using gas chromatograph-

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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- <i>tert</i> -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

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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 $\mu\text{g}/\text{m}^3$ and the quantitation limit is 343 $\mu\text{g}/\text{m}^3$. 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 Carboxen 1000/Carbosieve SIII 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 $\mu\text{g}/\text{m}^3$ for this method. Therefore, this method is useful for measuring 1,3-butadiene concentrations in the low ppb ($\mu\text{g}/\text{m}^3$) 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

7. ANALYTICAL METHODS

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 ($0.4 \mu\text{g}/\text{m}^3$ 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).

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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 ($\mu\text{g}/\text{m}^3$) 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 BMCL₁₀ 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](#).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

| Agency | Description | Information | Reference |
|-----------------------------|-----------------------------------|---|--------------------------|
| <u>INTERNATIONAL</u> | | | |
| 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 |
| <u>NATIONAL</u> | | | |
| 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 $\mu\text{g}/\text{m}^3$ | |
| 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 |

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

| Agency | Description | Information | Reference |
|-------------------------|--|---|----------------------------|
| <u>NATIONAL</u> (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 |
| | STEL (15-minutes) | 5 ppm | 29 CFR 1910.1051 |
| 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 |

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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 |

^aGroup 1: carcinogenic to humans

^bERPG-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).

^cAEGL-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).

^dBasis for listing: flammable gas

^eThe EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

^fA2: suspected human carcinogen

^gDesignated 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

9. REFERENCES

- Abdel-Rahman SZ, Ammenheuser MM, Omiecinski CJ, et al. 2005. Variability in human sensitivity to 1,3-butadiene: Influence of polymorphisms in the 5'-flanking region of the microsomal epoxide hydrolase gene (EPHX1). *Toxicol Sci* 85(1):624-631.
- Abdel-Rahman SZ, Ammenheuser MM, Ward JB. 2001. Human sensitivity to 1,3-butadiene: Role of microsomal epoxide hydrolase polymorphisms. *Carcinogenesis* 22(3):415-423.
- Abdel-Rahman SZ, El-Zein RA, Ammenheuser MM, et al. 2003. Variability in human sensitivity to 1,3-butadiene: Influence of the allelic variants of the microsomal epoxide hydrolase gene. *Environ Mol Mutagen* 41(2):140-146.
- ACGIH. 2008. 1,3-Butadiene. In: Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.
- Adam T, Mitsche S, Streibel T, et al. 2006. Puff-by-puff resolved characterisation of cigarette mainstream smoke by single photon ionisation (SPI)-time-of-flight mass spectrometry (TOFMS): Comparison of the 2R4F research cigarette and pure Burley, Virginia, Oriental and Maryland tobacco cigarettes. *Anal Chim Acta* 572(2):219-229.
- Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. *Dev Med Child Neurol* 27(4):532-537.
- Adler ID, Filser J, Gonda H, et al. 1998. Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. *Mutat Res* 397(1):85-92.
- Adler ID, Filser JG, Gassner P, et al. 1995a. Heritable translocations induced by inhalation exposure of male mice to 1,3-butadiene. *Mutat Res* 347(3-4):121-127.
- *Adler ID, Kliesch U, Tiveron C, et al. 1995b. Clastogenicity of diepoxybutane in bone marrow cells and male germ cells of mice. *Mutagenesis* 10(6):535-541.
- Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. *Environ Health Perspect Suppl* 103(7):103-112.
- Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Atlanta, GA. *Fed Regist* 54(174):37618-37634.
- AICHE. 2000. 1,3-Butadiene. C₄H₆. In: Physical and thermodynamic properties of pure chemicals. American Institute of Chemical Engineers, Design Institute for Physical Property Data. Philadelphia, PA: Taylor and Francis.
- AIHA. 2008. Emergency Response Planning Guidelines (ERPG). Fairfax, VA: American Industrial Hygiene Association. <http://www.aiha.org/documents/Committees/ERP-erpglevels.pdf>. May 19, 2009.

* Not cited in text

9. REFERENCES

- Albertini RJ, Carson ML, Kirman CR, et al. 2010. 1,3-Butadiene: II. Genotoxicity profile. *Crit Rev Toxicol* 40(Suppl 1):12-73.
- Albertini RJ, Sram RJ, Vacek PM, et al. 2001. Biomarkers for assessing occupational exposures to 1,3-butadiene. *Chem Biol Interact* 135-136:429-453.
- Albertini RJ, Sram RJ, Vacek PM, et al. 2007. Molecular epidemiological studies in 1,3-butadiene exposed Czech workers: Female-male comparisons. *Chem Biol Interact* 166(1-3):63-77.
- Albrecht OE, Filser JG, Neumann HG. 1993. Biological monitoring of 1,3-butadiene: Species differences in haemoglobin binding in rat and mouse. *IARC Sci Publ* 127:135-142.
- Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies of Experimental Biology.
- American Chemical Society. 2007. United States synthetic rubber program, 1939-1945. American Chemical Society. <http://acswebcontent.acs.org/landmarks/landmarks/rbb/index.html>. May 29, 2009.
- Ammenheuser MM, Bechtold WE, Abdel-Rahman SZ, et al. 2001. Assessment of 1,3-butadiene exposure in polymer production workers using *HPRT* mutations in lymphocytes as a biomarker. *Environ Health Perspect* 109(12):1249-1255.
- Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3(6):272-290.
- Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. *Animal test alternatives: Refinement, reduction, and replacement*. New York, NY: Marcel Dekker, Inc., 9-25.
- Andersen ME, Clewell HJ, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol Appl Pharmacol* 87(2):185-205.
- Anderson D, Edwards AJ, Brinkworth MH, et al. 1996. Male-mediated F₁ effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.
- Anderson D, Hughes JA, Edwards AJ, et al. 1998. A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. *Mutat Res* 397(1):77-84.
- Anttinen-Klemetti T, Vaaranrinta R, Mutanen P, et al. 2006. Inhalation exposure to 1,3-butadiene and styrene in styrene-butadiene copolymer production. *Int J Hyg Environ Health* 209(2):151-158.
- Arce GT, Vincent DR, Cunningham MJ, et al. 1989. The *in vitro* and *in vivo* genotoxicity of 1,3-butadiene and metabolites. Haskell Laboratory for Toxicology and Industrial Medicine, E.I. Du Pont de Nemours and Company, Inc.
- Atkinson R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. *J Phys Chem Ref Data* 1:110.

9. REFERENCES

- Atkinson R, Carter WPL. 1984. Kinetics and mechanisms of gas-phase reactions of ozone with organic compounds under atmospheric conditions. *Chem Rev* 84:437-470.
- Atkinson R, Aschmann SM, Winer AM, et al. 1984. Kinetics of the gas-phase reactions of NO³ radicals with a series of dialkenes, cycloalkenes, and monoterpenes at 295 ± 1K. *Environ Sci Technol* 18:370-375.
- Au WW, Bechtold WE, Whorton EB, et al. 1995. Chromosome aberrations and response to γ-ray challenge in lymphocytes of workers exposed to 1,3-butadiene. *Mutat Res* 334:125-130.
- Austin CC, Wang D, Ecobichon DJ, et al. 2001. Characterization of volatile organic compounds in smoke at municipal structural fires. *J Toxicol Environ Health A* 63(6):437-458.
- Autio K, Renzi L, Catalan J, et al. 1994. Induction of micronuclei in peripheral blood and bone marrow erythrocytes of rats and mice exposed to 1,3-butadiene by inhalation. *Mutat Res* 309(2):315-320.
- Baker J, Arey J, Atkinson R. 2005. Formation and reaction of hydroxycarbonyls from the reaction of OH radicals with 1,3-butadiene and isoprene. *Environ Sci Technol* 39(11):4091-4099.
- Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. *Regul Toxicol Pharmacol* 8(4):471-486.
- Bartle KD, Bergstedt L, Novotny M, et al. 1969. Tobacco chemistry II. Analysis of the gas phase of tobacco smoke by gas chromatography-mass spectrometry. *J Chromatogr* 45(2):256-263.
- Beaudouin R, Micallef S, Brochet C. 2010. A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan. *Regul Toxicol Pharmacol* 57(1):103-116.
- Bechtold WE, Strunk MR, Chang I, et al. 1994. Species differences in urinary butadiene metabolites: Comparisons of metabolite ratios between mice, rats, and humans. *Toxicol Appl Pharmacol* 127:44-49.
- Begemann P, Sram RJ, Neumann HG. 2001a. Hemoglobin adducts of epoxybutene in workers occupationally exposed to 1,3-butadiene. *Arch Toxicol* 74(11):680-687.
- Begemann P, Upton PB, Ranasinghe A, et al. 2001b. Hemoglobin adducts as biomarkers of 1,3-butadiene in occupationally low exposed Italian workers and a few diesel-exposed miners. *Chem Biol Interact* 135-136:675-678.
- Berger GS, ed. 1994. Epidemiology of endometriosis. In: *Endometriosis: Modern surgical management of endometriosis*. New York, NY: Springer-Verlag, 3-7.
- Bernardini S, Hirvonen A, Pelin K, et al. 1998. Induction of sister chromatid exchange by 1,2-epoxy-3-butene in cultured human lymphocytes: Influence of GSTT1 genotype. *Carcinogenesis* 19(2):377-380.
- Bevan C, Stadler JC, Elliott GS, et al. 1996. Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. *Fundam Appl Toxicol* 32(1):1-10.
- Biemer JJ. 1983. The preleukemic syndrome. *Ann Clin Lab Sci* 13(2):156-162.

9. REFERENCES

- Blomberg L, Widmark G. 1975. Separation of fresh tobacco on a packed polar gas chromatographic column prior to on-line analysis by gas chromatography-mass spectrometry using a non-polar capillary column. *J Chromatogr* 106(1):59-71.
- Bois FY, Smith TJ, Gelman A, et al. 1999. Optimal design for a study of butadiene toxicokinetics in humans. *Toxicol Sci* 49:213-224.
- Bolt HM, Filser JG, Stormer F. 1984. Inhalation pharmacokinetics based on gas uptake studies. V. Comparative pharmacokinetics of ethylene and 1,3-butadiene in rats. *Arch Toxicol* 55:213-218.
- Bolt HM, Schmiedel G, Filser JG, et al. 1983. Biological activation of 1,3-butadiene to vinyl oxirane by rat liver microsomes and expiration of the reactive metabolite by exposed rats. *J Cancer Res Clin Oncol* 106:112-116.
- Bond JA, Csanady GA, Leavens T, et al. 1993. Research strategy for assessing target tissue dosimetry of 1,3-butadiene in laboratory animals and humans. *IARC Sci Publ* (127):45-55.
- Bond JA, Dahl AR, Henderson RF, et al. 1986. Species differences in the disposition of inhaled butadiene. *Toxicol Appl Pharmacol* 84(3):617-627.
- Bond JA, Dahl AR, Henderson RF, et al. 1987. Species differences in the distribution of inhaled butadiene in tissues. *Am Ind Hyg Assoc J* 48(10):867-872.
- Bond JA, Himmelstein MW, Seaton M, et al. 1996. Metabolism of butadiene by mice, rats, and humans: A comparison of physiologically based toxicokinetic model predictions and experimental data. *Toxicology* 113(1-3):48-54.
- *Bond JA, Martin OS, Birnbaum LS, et al. 1988. Metabolism of 1,3-butadiene by lung and liver microsomes of rats and mice repeatedly exposed by inhalation to 1,3-butadiene. *Toxicol Lett* 44:143-151.
- Boogaard PJ, van Sittert NJ, Megens HJ. 2001a. Urinary metabolites and haemoglobin adducts as biomarkers of exposure to 1,3-butadiene: A basis for 1,3-butadiene cancer risk assessment. *Chem Biol Interact* 135-136:695-701.
- Boogaard PJ, van Sittert NJ, Watson WP, et al. 2001b. A novel DNA adduct, originating from 1,2-epoxy-3,4-butanediol, is the major DNA adduct after exposure to [2,3-¹⁴C]-1,3-butadiene,[4-¹⁴C]-1,2-epoxy-3-butane. *Chem Biol Interact* 135-136:687-693.
- Boysen G, Georgieva NI, Bordeerat NK, et al. 2012. Formation of 1,2:3,4-diepoxybutane-specific hemoglobin adducts in 1,3-butadiene exposed workers. *Toxicol Sci* 125:30-40.
- Boysen G, Georgieva NI, Upton PB, et al. 2004. Analysis of diepoxide-specific cyclic N-terminal globin adducts in mice and rats after inhalation exposure to 1,3-butadiene. *Cancer Res* 64(23):8517-8520.
- Brinkworth MH, Anderson D, Hughes JA, et al. 1998. Genetic effects of 1,3-butadiene on the mouse testis. *Mutat Res* 397(1):67-75.
- Brochot C, Bois FY. 2005. Use of a chemical probe to increase safety for human volunteers in toxicokinetic studies. *Risk Anal* 25(6):1559-1571.

9. REFERENCES

- Brochot C, Smith TJ, Bois FY. 2007. Development of a physiologically based toxicokinetic model for butadiene and four major metabolites in humans: Global sensitivity analysis for experimental design issues. *Chem Biol Interact* 167(3):168-183.
- Broderick BM, Marnane IS. 2002. A comparison of the C₂-C₉ hydrocarbon compositions of vehicle fuels and urban air in Dublin, Ireland. *Atmos Environ* 36:975-986.
- Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: C.V. Mosby Company, 226-227.
- Brunnemann KD, Kagan MR, Cox JE, et al. 1990. Analysis of 1,3-butadiene and other selected gas-phase components in cigarette mainstream and sidestream smoke by gas chromatography-mass selective detection. *Carcinogenesis* 11(10):1863-1868.
- Carmella SG, Chen M, Han S, et al. 2009. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. *Chem Res Toxicol* 22(4):734-741.
- Carpenter CP, Shaffer CB, Weil CS, et al. 1944. Studies on the inhalation of 1:3-butadiene; with a comparison of its narcotic effect with benzol, toluol, and styrene, and a note on the elimination of styrene by the human. *J Ind Hyg Toxicol* 26:69-78.
- Carrieri M, Bartolucci GB, Livieri M, et al. 2009. Quantitative determination of the 1,3-butadiene urinary metabolite 1,2-dihydroxybutyl mercapturic acid by high-performance liquid chromatography/tandem mass spectrometry using polynomial calibration curves. *J Chromatogr B Analyt Technol Biomed Life Sci* 877:1388-1393.
- Case RAM, Hosker ME. 1954. Tumour of the urinary bladder as an occupational disease in the rubber industry in England and Wales. *Br J Prev Soc Med* 8:39-50.
- Checkoway H, Williams TM. 1982. A hematology survey of workers at a styrene-butadiene synthetic rubber manufacturing plant. *Am Ind Hyg Assoc J* 43:164-169.
- Chemical Market Reporter. 2006. Chemical profile: Butadiene. *Chem Market Rep* May 22-28 2006:34.
- Chemical Week. 2008. Product focus: Butadiene. *Chem Week* March 10:31.
- ChemID Plus Advanced. 2009. 1,3-Butadiene. ChemIDplus. Bethesda, MD: U.S. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/>. June 1, 2009.
- Cheng H, Sathiakumar N, Graff J, et al. 2007. 1,3-Butadiene and leukemia among synthetic rubber industry workers: Exposure-response relationships. *Chem Biol Interact* 166(1-3):15-24.
- Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. *Toxicol Ind Health* 1(4):111-131.
- Cochrane JE, Skopek TR. 1993. Mutagenicity of 1,3-butadiene and its epoxide metabolites in human TK6 cells and in splenic T cells isolated from exposed B6C3F₁ mice. In: Sorsa M, Peltonen K, Vainio H, et al., eds. Butadiene and styrene: Assessment of health hazards. IARC Scientific Publications No. 127. Lyon, France: International Agency for Research on Cancer, 195-204.

9. REFERENCES

- Counts ME, Hsu FS, Tewes FJ. 2006. Development of a commercial cigarette "market map" comparison methodology for evaluating new or non-conventional cigarettes. *Regul Toxicol Pharmacol* 46:225-242.
- Cowles SR, Tsai SP, Snyder PJ, et al. 1994. Mortality, morbidity, and haematological results from a cohort of long-term workers involved in 1,3-butadiene monomer production. *Occup Environ Med* 51(5):323-329.
- Crouch CN, Pullinger DH, Gaunt IF. 1979. Inhalation toxicity studies with 1,3-butadiene 2. 3 month toxicity study in rats. *Am Ind Hyg Assoc J* 40:796-802.
- Csanady GA, Guengerich FP, Bond JA. 1992. Comparison of the biotransformation of 1,3-butadiene and its metabolite, butadiene monoepoxide, by hepatic and pulmonary tissues from humans, rats and mice. *Carcinogenesis* 13(7):1143-1153.
- Csanady GA, Kreuzer PE, Baur C, et al. 1996. A physiological toxicokinetic model for 1,3-butadiene in rodents and man: Blood concentrations of 1,3-butadiene, its metabolically formed epoxides, and of haemoglobin adducts—relevance of glutathione depletion. *Toxicology* 113(1-3):300-305.
- Cunningham MJ, Choy WN, Arce GT, et al. 1986. *In vivo* sister chromatid exchange and micronucleus induction studies with 1,3-butadiene in B6C3F₁ mice and Sprague-Dawley rats. *Mutagenesis* 1(6):449-452.
- Currance PL, Clements B, Bronstein AC. 2007. Aliphatic hydrocarbons and related compounds. In: Honeycutt L, ed. *Emergency care for hazardous materials exposure*. 3rd ed. St. Louis, MO: Mosby/Jems, 240-242.
- Curren KC, Dann TF, Wang DK. 2006. Ambient air 1,3-butadiene concentrations in Canada (1995-2003): Seasonal, day of week variations, trends, and source influences. *Atmos Environ* 40:170-181.
- Dahl AR, Bechtold WE, Bond JA, et al. 1990. Species differences in the metabolism and disposition of inhaled 1,3-butadiene and isoprene. *Environ Health Perspect* 86:65-69.
- Dahl AR, Sun JD, Birnbaum LS, et al. 1991. Toxicokinetics of inhaled 1,3-butadiene in monkeys: Comparison to toxicokinetics in rats and mice. *Toxicol Appl Pharmacol* 110(1):9-19.
- Delzell E, Macaluso M, Sathiakumar N, et al. 2001. Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. *Chem Biol Interact* 135-136:515-534.
- Delzell E, Sathiakumar N, Hovinga M, et al. 1996. A follow-up study of synthetic rubber workers. *Toxicology* 113(1-3):182-189.
- de Meester C. 1988. Genotoxic properties of 1,3-butadiene. *Mutat Res* 195(104):273-281.
- de Meester C, Poncelet F, Roberfroid M, et al. 1978. Mutagenicity of butadiene and butadiene monoxide. *Biochem Biophys Res Commun* 80(2):298-305.
- de Meester C, Poncelet F, Roberfroid M, et al. 1980. The mutagenicity of butadiene towards *Salmonella typhimurium*. *Toxicol Lett* 6(3):125-130.

9. REFERENCES

- Deutschmann S, Laib RJ. 1989. Concentration-dependent depletion of non-protein sulfhydryl (NPSH) content in lung, heart and liver tissues of rats and mice after acute inhalation exposure to butadiene. *Toxicol Lett* 45:175-183.
- Divine BJ. 1989. An update on mortality among workers at a butadiene facility—preliminary results. Report by Texaco Inc., Houston, TX.
- Divine BJ. 1990. An update on mortality among workers at a 1,3-butadiene facility — preliminary results. *Environ Health Perspect* 86:119-128.
- Divine BJ, Hartman CM. 1996. Mortality update of butadiene production workers. *Toxicology* 113(1-3):169-181.
- Divine BJ, Hartman CM. 2001. A cohort mortality study among workers at a 1,3 butadiene facility. *Chem Biol Interact* 135-136:535-553.
- Divine BJ, Wendt JK, Hartman CM. 1993. Cancer mortality among workers at a butadiene production facility. In: Sorsa M, Peltonen K, Vainio H, et al., eds. *Butadiene and styrene: Assessment of health hazards*. IARC Scientific Publications No. 127. Lyon, France: International Agency for Research on Cancer, 345-362.
- DOE/NTP. 1987a. Inhalation developmental toxicology studies of 1,3-butadiene in the rat. Final report. Richland, WA: U.S. Department of Energy. National Toxicology Program. PNL6414. DE88004186.
- DOE/NTP. 1987b. Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice. Final report. U.S. Department of Energy. National Toxicology Program. PNL6412. DE88004187.
- DOE/NTP. 1988a. Sperm-head morphology study in B6C3F₁ mice following inhalation exposure to 1,3-butadiene. Final technical report. Richland, WA: U.S. Department of Energy. National Toxicology Program. PNL6459. DE88008620.
- DOE/NTP. 1988b. Dominant lethal study in CD-1 mice following inhalation exposure to 1,3-butadiene: Final technical report. Richmond, WA: U.S. Department of Energy. National Toxicology Program. PNL6545. DE88010185.
- Doerr JK, Hollis EA, Sipes IG. 1996. Species difference in the ovarian toxicity of 1,3-butadiene epoxides in B6C3F₁ mice and Sprague-Dawley rats. *Toxicology* 113:128-136.
- Dolnick AA, Potash M. 1948. Butadiene. In: Kirk RE, Othmer DF, eds. *Kirk-Othmer encyclopedia of chemical technology*. Vol. 2. New York, NY: Interscience Encyclopedias, Inc., 669-674.
- Downs TD, Crane MM, Kim KW. 1987. Mortality among workers at a butadiene facility. *Am J Ind Med* 12:311-329.
- Duescher RJ, Elfarra AA. 1994. Human liver microsomes are efficient catalysts of 1,3-butadiene oxidation: Evidence for major roles by cytochromes P450 2A6 and 2E1. *Arch Biochem Biophys* 311(2):342-349.
- Elfarra AA, Krause RJ, Kemper RA. 2001. Cellular and molecular basis for species, sex and tissue differences in 1,3-butadiene metabolism. *Chem Biol Interact* 135-136:239-248.

9. REFERENCES

Elfarra AA, Krause RJ, Selzer RR. 1996. Biochemistry of 1,3-butadiene metabolism and its relevance to 1,3-butadiene-induced carcinogenicity. *Toxicology* 113(1-3):23-30.

EPA. 1978. Interim primary drinking water regulations. U.S. Environmental Protection Agency. Fed Regist 43:29135-29150.

EPA. 1982. Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA600/1482057.

EPA. 1985. Mutagenicity and carcinogenicity assessment of 1,3-butadiene. Washington, DC: U.S. Environmental Protection Agency. EPA600/885004F.

EPA. 1986. Methods for the determination of organic compounds in finished drinking water and raw source water. Cincinnati, OH: U.S. Environmental Protection Agency, Physical and Chemical Methods Branch.

EPA. 1988a. Guidelines establishing test procedures for the analysis of pollutants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 1:36, 249-267.

*EPA 1988b. Protection of environment. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355:182-191.

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency. EPA600/890066F.

EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630/R96012.

EPA. 1999a. Compendium of methods for the determination of toxic organic compounds in ambient air. Second edition. Compendium method TO-15. Determination of volatile organic compounds (VOCs) in air collected in specially-prepared canisters and analyzed by gas chromatography/mass spectrometry (GC/MS). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA625/R96010b.

EPA. 1999b. Compendium of methods for determination of toxic organic compounds in ambient air. Second edition. Compendium method TO-14A. Determination of volatile organic compounds (VOCs) in ambient air using specially prepared canisters with subsequent analysis by gas chromatography. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA625/R96010b

EPA. 2002. Health assessment of 1,3-butadiene. Washington, DC: U.S. Environmental Protection Agency. EPA600/P98001F.

EPA. 2003a. Estimate background concentrations for the national-scale air toxics assessment. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards.

9. REFERENCES

- EPA. 2003b. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. Office of Ground Water and Drinking Water, <http://www.epa.gov/safewater/contaminants/index.html>. May 19, 2009.
- EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.
- EPA. 2006a. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822R04005. <http://epa.gov/waterscience/criteria/drinking/>. May 19, 2009.
- EPA. 2006b. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency. Office of Water, Office of Science and Technology, <http://www.epa.gov/waterscience/criteria/wqcriteria.html>. May 11, 2009.
- EPA. 2008. 2005 National emissions inventory data & documentation. National Emissions Inventory. U.S. Environmental Protection Agency. <http://www.epa.gov/ttn/chief/net/2005inventory.html>. May 26, 2009.
- EPA. 2009a. Acute exposure guideline levels (AEGLs). Washington, DC: U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/aegl/>. May 19, 2009.
- EPA. 2009b. Hazardous air pollutants. Clean Air Act. U.S. Environmental Protection Agency. United States Code. 42 USC 7412. <http://www.epa.gov/ttn/atw/orig189.html>. May 19, 2009.
- EPA. 2009c. Regulated toxic substances and threshold quantities for accidental release prevention. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 68.130. <http://www.epa.gov/lawsregs/search/40cfr.html>. May 20, 2009.
- EPA. 2009d. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notifications. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. <http://www.epa.gov/lawsregs/search/40cfr.html>. May 20, 2009.
- EPA. 2009e. Superfund, emergency planning, and community right-to-know programs. Toxic chemical release reporting. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. <http://www.epa.gov/lawsregs/search/40cfr.html>. May 11, 2009.
- Evelo CTA, Oostendorp JGM, ten Berge WF, et al. 1993. Physiologically based toxicokinetic modeling of 1,3-butadiene lung metabolism in mice becomes more important at low doses. *Environ Health Perspect* 101(6):496-502.
- FDA. 2008. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. <http://vm.cfsan.fda.gov/~dms/eafus.html>. May 19, 2009.
- FEDRIP. 2009. Federal Research in Progress Database. Springfield, VA: National Technical Information Service.

9. REFERENCES

- Filser JG, Bolt HM. 1984. Inhalation pharmacokinetics based on gas uptake studies. VI. Comparative evaluation of ethylene oxide and butadiene monoxide as exhaled reactive metabolites of ethylene and 1,3-butadiene in rats. *Arch Toxicol* 55(4):219-223.
- Filser JG, Bhowmik S, Faller TH, et al. 2010. Quantitative investigation on the metabolism of 1,3-butadiene and of its oxidized metabolites in once-through perfused livers of mice and rats. *Toxicol Sci* 114(1):25-37.
- Filser JG, Faller TH, Bhowmik S, et al. 2001. First-pass metabolism of 1,3-butadiene in once-through perfused livers of rats and mice. *Chem Biol Interact* 135-136:249-265.
- Filser JG, Hutzler C, Meischner V, et al. 2007. Metabolism of 1,3-butadiene to toxicologically relevant metabolites in single-exposed mice and rats. *Chem Biol Interact* 166(1-3):93-103.
- Filser JG, Johanson G, Kessler W, et al. 1993. A pharmacokinetic model to describe toxicokinetic interactions between 1,3-butadiene and styrene in rats: Predictions for human exposure. In: Sorsa M, Peltonen K, Vainio H, et al., eds. *Butadiene and styrene: Assessment of health hazards*. IARC Scientific Publications No. 127. Lyon, France: International Agency for Research on Cancer, 65-78.
- Fomon SJ. 1966. Body composition of the infant: Part I: The male reference infant. In: Falkner F, ed. *Human development*. Philadelphia, PA: WB Saunders, 239-246.
- Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr* 35(Suppl 5):1169-1175.
- Fox AJ, Lindars DC, Owen R. 1974. A survey of occupational cancer in the rubber and cablemaking industries: Results of five-year analysis, 1976-71. *Br J Ind Med* 31(2):140-151.
- Fustinoni S, Perbellini L, Soleo L, et al. 2004. Biological monitoring in occupational exposure to low levels of 1,3-butadiene. *Toxicol Lett* 149(1-3):353-360.
- Georgieva NI, Boysen G, Bordeerat N, et al. 2010. Exposure-response of 1,2,3,4-diepoxybutane-specific N-terminal valine adducts in mice and rats after inhalation exposure to 1,3-butadiene. *Toxicol Sci* 115(2):322-329.
- Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. *Environ Health Perspect* 101(Suppl 2):65-71.
- Goggin M, Swenberg JA, Walker VE, et al. 2009. Molecular dosimetry of 1,2,3,4-diepoxybutane-induced DNA — DNA cross-links in B6C3F₁ mice and F344 rats exposed to 1,3-butadiene by inhalation. *Cancer Res* 69(6):2479-2486.
- Graff JJ, Sathlakumar N, Macaluso M, et al. 2005. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. *J Occup Med* 47:916-932.
- Graff JJ, Sathlakumar N, Macaluso M, et al. 2009. The effect of uncertainty in exposure estimation on the exposure-response relation between 1,3-butadiene and leukemia. *Int J Environ Res Public Health* 6(9):2436-2455.
- Graham LA, Noseworthy L, Fugler D, et al. 2004. Contribution of vehicle emissions from an attached garage to residential indoor air pollution levels. *J Air Waste Manage Assoc* 54(5):563-584.

9. REFERENCES

- Grant RL, Haney J, Curry AL, et al. 2010. A chronic reference value for 1,3-butadiene based on an updated noncancer toxicity assessment. *J Toxicol Environ Health B Crit Rev* 13(6):460-475.
- Grant RL, Leopold V, McCant D, et al. 2007. Spatial and temporal trend evaluation of ambient concentrations of 1,3-butadiene and chloroprene in Texas. *Chem Biol Interact* 166(1-3):44-51.
- Green T, Toghiani A, Moore R. 2001. The influence of co-exposure to dimethyldithiocarbamate on butadiene metabolism. *Chem Biol Interact* 135-136:585-598.
- Grub J, Loser E. 2005. Butadiene. In: *Ullmann's encyclopedia of industrial chemistry*, 1-17. http://mrw.interscience.wiley.com/emrw/9783527306732/ueic/article/a04_431/current/pdf. May 31, 2009.
- Gustafson P, Barregard L, Strandberg B, et al. 2007. The impact of domestic wood burning on personal, indoor and outdoor levels of 1,3-butadiene, benzene, formaldehyde and acetaldehyde. *J Environ Monit* 9(1):23-32.
- Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences and Press Institute Press.
- Hallberg LM, Bechtold WE, Grady J, et al. 1997. Abnormal DNA repair activities in lymphocytes of workers exposed to 1,3-butadiene. *Mutat Res* 383(3):213-221.
- Hansch C, Leo A, Hoekman D. 1995. Exploring QSAR hydrophobic, electronic, and steric constants. Washington, DC: American Chemical Society, 8.
- Hayes RB, Xi L, Bechtold WE, et al. 1996. *hprt* Mutation frequency among workers exposed to 1,3-butadiene in China. *Toxicology* 113(1-3):100-105.
- Hayes RB, Zhang L, Swenberg JA, et al. 2001. Markers for carcinogenicity among butadiene-polymer workers in China. *Chem Biol Interact* 135-136:455-464.
- Hayes RB, Zhang L, Yin S, et al. 2000. Genotoxic markers among butadiene polymer workers in China. *Carcinogenesis* 21(1):55-62.
- HazDat. 2007. 1,3-Butadiene. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry.
- Health Canada. 2000. Canadian Environmental Protection Act, 1999. Priority substances list health assessment: 1,3-Butadiene. Health Canada. Environment Canada. Minister of Public Works and Government Services. http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/1_3_butadiene/index-eng.php. July 9, 2009.
- HEI. 2000. 1,3-Butadiene: cancer, mutations, and adducts. Number 92. Cambridge, MA: Health Effects Institute.
- HEI. 2003. Biomarkers in Czech workers exposed to 1,3-butadiene: A transitional epidemiologic study. Number 116. Boston, MA: Health Effects Institute.
- HEI. 2006. An updated study of mortality among North American synthetic rubber industry workers. Number 132. Boston, MA: Health Effects Institute.

9. REFERENCES

- Henderson RF, Thornton-Manning JR, Bechtold WE, et al. 1996. Metabolism of 1,3-butadiene: Species differences. *Toxicology* 113(1-3):17-22.
- Hendricks WD, Schultz GR. 1986. A sampling and analytical method for monitoring low ppm air concentrations of 1,3-butadiene. *Appl Ind Hyg* 1:186-189.
- Higashino H, Mita K, Yoshikado H, et al. 2007. Exposure and risk assessment of 1,3-butadiene in Japan. *Chem Biol Interact* 166(1-3):52-62.
- Himmelstein MW, Acquavella JF, Recio L, et al. 1997. Toxicology and epidemiology of 1,3-butadiene. *Crit Rev Toxicol* 27(1):1-108.
- Himmelstein MW, Asgharian B, Bond JA. 1995. High concentrations of butadiene epoxides in livers and lungs of mice compared to rats exposed to 1,3-butadiene. *Toxicol Appl Pharmacol* 132(2):281-288.
- Himmelstein MW, Turner MJ, Asgharian B, et al. 1994. Comparison of blood concentrations of 1,3-butadiene and butadiene epoxides in mice and rats exposed to 1,3-butadiene by inhalation. *Carcinogenesis* 15(8):1479-1486.
- Himmelstein MW, Turner MJ, Asgharian B, et al. 1996. Metabolism of 1,3-butadiene: Inhalation pharmacokinetics and tissue dosimetry of butadiene epoxides in rats and mice. *Toxicology* 113(1-3):306-309.
- Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. *J Natl Cancer Inst* 84(5):313-320.
- Hong HH, Devereux TR, Melnick RL, et al. 2000. Mutations of *ras* protooncogenes and *p53* tumor suppressor gene in cardiac hemangiosarcomas from B6C3F₁ mice exposed to 1,3-butadiene for 2 years. *Toxicol Pathol* 28(4):529-534.
- Hou CT, Patel R, Laskin AI, et al. 1979. Microbial oxidation of gaseous hydrocarbons: Epoxidation of C₂ to C₄ n-alkenes by methylotrophic bacteria. *Appl Environ Microbiol* 38:127-134.
- Hou CT, Patel R, Laskin AI, et al. 1983. Epoxidation of short-chain alkenes by resting-cell suspensions of propane-grown bacteria. *Appl Environ Microbiol* 46:171-177.
- HSDB. 2009. 1,3-butadiene. Hazardous Substances Data Bank. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>. April 7, 2009.
- Hughes K, Meek ME, Walker M, et al. 2003. 1,3-Butadiene: Exposure estimation, hazard characterization, and exposure-response analysis. *J Toxicol Environ Health B Crit Rev* 6(1):55-83.
- Hurst HE. 2007. Toxicology of 1,3-butadiene, chloroprene, and isoprene. *Rev Environ Contam Toxicol* 189:131-179.
- IARC. 2009. Agents reviewed by the IARC Monographs. Volumes 1-99. Lyon, France: International Agency for Research on Cancer. <http://monographs.iarc.fr/ENG/Classification/index.php>. May 19, 2009.
- ICIS. 2009. Butadiene uses and market data. <http://www.icis.com/v2/chemicals/9075172/butadiene/uses.html>. June 1, 2009.

9. REFERENCES

- IRIS. 2012. 1,3-Butadiene. Washington, DC: Integrated Risk Information System. <http://www.epa.gov/iris/subst/index.html>. September 5, 2012.
- Irons RD, Pyatt DW. 1998. Dithiocarbamates as potential confounders in butadiene epidemiology. *Carcinogenesis* 19(4):539-542.
- Irons RD, Oshimura M, Barrett JC. 1987b. Chromosome aberrations in mouse bone marrow cells following *in vivo* exposure to 1,3-butadiene. *Carcinogenesis* 8(11):1711-1714.
- Irons RD, Smith CN, Stillman WS, et al. 1986a. Macrocytic-megaloblastic anemia in male B6C3F₁ mice following chronic exposure to 1,3-butadiene. *Toxicol Appl Pharmacol* 83(1):95-100.
- Irons RD, Smith CN, Stillman WS, et al. 1986b. Macrocytic-megaloblastic anemia in male NIH Swiss mice following repeated exposure to 1,3-butadiene. *Toxicol Appl Pharmacol* 85(3):450-455.
- *Irons RD, Stillman WS, Cloyd MW. 1987a. Selective activation of endogenous ecotropic retrovirus in hematopoietic tissues of B6C3F₁ mice during the preleukemic phase of 1,3-butadiene exposure. *Virology* 161(2):457-462.
- Irons RD, Stillman WS, Pyatt DW, et al. 2001. Comparative toxicity of dithiocarbamates and butadiene metabolites in human lymphoid and bone marrow cells. *Chem Biol Interact* 135-136:615-625.
- Irvine LFH. 1981. 1,3-Butadiene: Inhalation teratogenicity study in the rat. Final report. Harrogate, England: Hazleton Laboratories Europe Ltd. OTS050545.
- *Jackson MA, Stack HF, Rice JM, et al. 2000a. A review of the genetic and related effects of 1,3-butadiene in rodents and humans. *Mutat Res* 463(3):181-213.
- Jackson TE, Lilly PD, Recio L, et al. 2000b. Inhibition of cytochrome P450 2E1 decreases, but does not eliminate, genotoxicity mediated by 1,3-butadiene. *Toxicol Sci* 55(2):266-273.
- Jauhar PP, Henika PR, Macgregor JT, et al. 1988. 1,3-Butadiene: Induction of micronucleated erythrocytes in the peripheral blood of B6C3F₁ mice exposed by inhalation for 13 weeks. *Mutat Res* 209(3-4):171-176.
- Jelitto B, Vangala RR, Laib RJ. 1989. Species differences in DNA damage by butadiene: Role of diepoxybutane. *Arch Toxicol Suppl* 13:246-249.
- Johanson G, Filser JG. 1993. A physiologically based pharmacokinetic model for butadiene and its metabolite butadiene monoxide in rat and mouse and its significance for risk extrapolation. *Arch Toxicol* 67(3):151-163.
- Johanson G, Filser JG. 1996. PBPK model for butadiene metabolism to epoxides: Quantitative species differences in metabolism. *Toxicology* 113(1-3):40-47.
- Jones B, Harris RL. 1983. Calculation of time-weighted average concentrations: A computer mapping application. *Am Ind Hyg Assoc J* 44:795-801.
- Junk GA, Ford CS. 1980. A review of organic emissions from selected combustion processes. *Chemosphere* 9:187-230.

9. REFERENCES

- Kelsey KT, Wiencke JK, Ward J, et al. 1995. Sister-chromatid exchanges, glutathione S-transferase θ deletion and cytogenetic sensitivity to diepoxybutane in lymphocytes from butadiene monomer production workers. *Mutat Res* 335(3):267-273.
- Kennedy CH, Catallo WJ, Wilson VL, et al. 2009. Combustion products of 1,3-butadiene inhibit catalase activity and induce expression of oxidative DNA damage repair enzymes in human bronchial epithelial cells. *Cell Biol Toxicol* 25(5):457-470.
- *Khalil M, Abudiab M, Ahmed AE. 2007. Clinical evaluation of 1,3-butadiene neurotoxicity in humans. *Toxicol Ind Health* 23(3):141-146.
- Kim SR, Dominici F, Buckley TJ. 2007. Concentrations of vehicle-related air pollutants in an urban parking garage. *Environ Res* 105(3):291-299.
- Kim Y, Hong HH, Lachat Y, et al. 2005. Genetic alterations in brain tumors following 1,3-butadiene exposure in B6C3F₁ mice. *Toxicol Pathol* 33(3):307-312.
- Kim YM, Harrad S, Harrison RM. 1999. An improved method for the determination of 1,3-butadiene in nonoccupational environments. *Environ Sci Technol* 33:4342-4345.
- Kim YM, Harrad S, Harrison RM. 2001. Concentrations and sources of VOCs in urban domestic and public microenvironments. *Environ Sci Technol* 35(6):997-1004.
- Kim YM, Harrad S, Harrison RM. 2002. Levels and sources of personal inhalation exposure to volatile organic compounds. *Environ Sci Technol* 36(24):5405-5410.
- Kirman CR, Grant RL. 2012. Quantitative human health risk assessment for 1,3-butadiene based upon ovarian effects in rodents. *Regul Toxicol Pharmacol* 62(2):371-384.
- Kirman CR, Albertini RA, Gargas ML. 2010b. 1,3-Butadiene: III. Assessing carcinogenic modes of action. *Crit Rev Toxicol* 40(Suppl 1):74-92.
- Kirman CR, Albertini RJ, Sweeney LM, et al. 2010a. 1,3-Butadiene: I. Review of metabolism and the implications to human health risk assessment. *Crit Rev Toxicol* 40(Suppl 1):1-11.
- Kirshenbaum I. 1978. Butadiene. In: Kirk-Othmer encyclopedia of chemical technology. Vol. 4. New York, NY: John Wiley & Sons, 313-337.
- Kligerman AD, DeMarini DM, Doerr CL, et al. 1999. Comparison of cytogenetic effects of 3,4-epoxy-1-butene and 1,2:3, 4-diepoxybutane in mouse, rat and human lymphocytes following *in vitro* G₀ exposures. *Mutat Res* 439(1):13-23.
- Knox EG. 2005. Childhood cancers and atmospheric carcinogens. *J Epidemiol Community Health* 59:101-105.
- Knox EG. 2006. Roads, railways, and childhood cancers. *J Epidemiol Community Health* 60(2):136-141.
- Kohn MC. 1997. The importance of anatomical realism for validation of physiological models of disposition of inhaled toxicants. *Toxicol Appl Pharmacol* 147:448-458.

9. REFERENCES

- Kohn MC, Melnick RL. 1993. Species differences in the production and clearance of 1,3-butadiene metabolites: A mechanistic model indicates predominantly physiological, not biochemical, control. *Carcinogenesis* 14(4):619-628.
- Kohn MC, Melnick RL. 1996. Effects of the structure of a toxicokinetic model of butadiene inhalation exposure on computed production of carcinogenic intermediates. *Toxicology* 113(1-3):31-39.
- Kohn MC, Melnick RL. 2000. The privileged access model of 1,3-butadiene disposition. *Environ Health Perspect* 108(Suppl 5):911-917.
- Kohn MC, Melnick RL. 2001. Physiological modeling of butadiene disposition in mice and rats. *Chem Biol Interact* 135-136:285-301.
- Koivisto P, Peltonen K. 2001. N7-guanine adducts of the epoxy metabolites of 1,3-butadiene in mice lung. *Chem Biol Interact* 135-136:363-372.
- Koturbash I, Scherhag A, Sorrentino J, et al. 2011b. Epigenetic alterations in liver of C57BL/6J mice after short-term inhalational exposure to 1,3-butadiene. *Environ Health Perspect* 119(5):635-640.
- Koturbash I, Scherhag A, Sorrentino J, et al. 2011a. Epigenetic mechanisms of mouse inter-strain variability in genotoxicity of the environmental toxicant 1,3-butadiene. *Toxicol Sci* 122(2):448-456.
- Krause RJ, Elfarra AA. 1997. Oxidation of butadiene monoxide to *meso*- and (+/-)-diepoxybutane by cDNA-expressed human cytochrome P450s and by mouse, rat, and human liver microsomes: evidence for preferential hydration of *meso*-diepoxybutane in rat and human liver microsomes. *Arch Biochem Biophys* 337(2):176-184.
- Kraybill HF. 1980. Evaluation of public health aspects of carcinogenic/mutagenic biorefractories in drinking water. *Prev Med* 9:212-218.
- Kreiling R, Laib RJ, Bolt HM. 1986a. Alkylation of nuclear proteins and DNA after exposure of rats and mice to carbon-14 1,3-butadiene. *Toxicol Lett* 30(2):131-136.
- Kreiling R, Laib RJ, Bolt HM. 1988. Depletion of hepatic non-protein sulfhydryl content during exposure of rats and mice to butadiene. *Toxicol Lett* 41(3):209-214.
- Kreiling R, Laib RJ, Filser JG, et al. 1986b. Species differences in butadiene metabolism between mice and rats evaluated by inhalation pharmacokinetics. *Arch Toxicol* 58(4):235-238.
- Kreiling R, Laib RJ, Filser JG, et al. 1987. Inhalation pharmacokinetics of 1,2-epoxybutene-3 reveal species differences between rats and mice sensitive to butadiene-induced carcinogenesis. *Arch Toxicol* 61(1):7-11.
- Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. *Principles and methods of toxicology*. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.
- Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. *Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches*. San Diego, CA: Academic Press, 399-437.

9. REFERENCES

- Lahdetie J, Peltonen K, Sjoblom T. 1997. Germ cell mutagenicity of three metabolites of 1,3-butadiene in the rat: Induction of spermatid micronuclei by butadiene mono-, di-, and diepoxides *in vivo*. *Environ Mol Mutagen* 29(3):230-239.
- Laib RJ, Filser JG, Kreiling R. 1988. Species differences in butadiene metabolism between mouse and rat. *Ann N Y Acad Sci* 534:663-670.
- Laib RJ, Filser JG, Kreiling R, et al. 1990. Inhalation pharmacokinetics of 1,3-butadiene and 1,2-epoxybutene-3 in rats and mice. *Environ Health Perspect* 86:57-63.
- Laib RJ, Tucholski M, Filser JG, et al. 1992. Pharmacokinetic interaction between 1,3-butadiene and styrene in Sprague-Dawley rats. *Arch Toxicol* 66(5):310-314.
- Leavens TL, Bond JA. 1996. Pharmacokinetic model describing the disposition of butadiene and styrene in mice. *Toxicology* 113(1-3):310-313.
- Leavens TL, Farris GM, James RA, et al. 1997. Genotoxicity and cytotoxicity in male B6C3F₁ mice following exposure to mixtures of 1,3-butadiene and styrene. *Environ Mol Mutagen* 29(4):335-345.
- Leavens TL, Moss OR, Turner MJ, et al. 1996. Metabolic interactions of 1,3-butadiene and styrene in male B6C3F₁ mice. *Toxicol Appl Pharmacol* 141(2):628-636.
- Leber AP. 2001. Human exposures to monomers resulting from consumer contact with polymers. *Chem Biol Interact* 135-136:215-220.
- Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. *Pediatr Clin North Am* 44(1):55-77.
- Leiderman LJ, Stillman WS, Shah RS, et al. 1986. Altered hematopoietic stem cell development in male B6C3F₁ mice following exposure to 1,3-butadiene. *Exp Mol Pathol* 44(1):50-56.
- Leikin JB, Paloucek FP. 2002. Leikin & Paloucek's poisoning & toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 306.
- Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantyne B, Marrs T, Turner P, eds. *General and applied toxicology*. Vol. 1. New York, NY: Stockton Press, 153-164.
- Lewis RJ. 2007. 1,3-Butadiene. In: Lewis RJ, ed. *Hawley's condensed chemical dictionary*. 5th ed. New York, NY: John Wiley & Sons, Inc., 190.
- Lide DR. 2008. Physical constants of organic compounds. In: Lide DR, ed. *CRC handbook of chemistry and physics*. 88th ed. New York, NY: CRC Press, 3-72.
- Lin YS, Smith TJ, Kelsey KT, et al. 2001. Human physiologic factors in respiratory uptake of 1,3-butadiene. *Environ Health Perspect* 109(9):921-926.
- Lin YS, Smith TJ, Wypij D, et al. 2002. Association of the blood/air partition coefficient of 1,3-butadiene with blood lipids and albumin. *Environ Health Perspect* 110(2):165-168.

9. REFERENCES

- Liu S, Ao L, Du B, et al. 2008. *HPRT* mutations in lymphocytes from 1,3-butadiene-exposed workers in China. *Environ Health Perspect* 116:203-208.
- Livingston AL. 1978. Forage plant estrogens. *J Toxicol Environ Health* 4(2-3):301-324.
- Lofroth G, Burton RM, Forehand L, et al. 1989. Characterization of environmental tobacco smoke. *Environ Sci Technol* 23(5):610-614.
- Lonneman WA, Namie GR, Bufalini JJ. 1979. Hydrocarbons in Houston air. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600/3-79-018, 36.
- Loprieno N, Presciuttini S, Sbrana I, et al. 1978. Mutagenicity of industrial compounds. VII. Styrene and styrene oxide: II. Point mutations, chromosome aberrations and DNA repair induction analyses. *Scand J Work Environ Health* 4:169-178.
- Lovreglio P, Bukvic N, Fustinoni S, et al. 2006. Lack of genotoxic effect in workers exposed to very low doses of 1,3-butadiene. *Arch Toxicol* 80(6):378-381.
- Lunsford RA. 1987. Comments on sampling and analytical method for monitoring low ppm air concentrations of 1,3-butadiene. *Appl Ind Hyg* 2:93-94.
- Lunsford RA, Gagnon YT. 1987. Use of a backflushable pre-column to maintain the performance of an aluminum oxide porous-layer open-tubular fused silica column for the determination of 1,3-butadiene in air. *J High Resolut Chromatogr* 10:102-104.
- Lyman WJ, Reehl WF, Rosenblatt DH. 1990. In: Handbook of chemical property estimation methods. Washington, DC: American Chemical Society, 15-15 to 15-17.
- Ma H, Wood TG, Ammenheuser MM, et al. 2000. Molecular analysis of *hprt* mutant lymphocytes from 1,3-butadiene-exposed workers. *Environ Mol Mutagen* 36(1):59-71.
- Macaluso M, Larson R, Delzell E, et al. 1996. Leukemia and cumulative exposure to butadiene, styrene and benzene among workers in the synthetic rubber industry. *Toxicology* 113(1-3):190-202.
- Macaluso M, Larson R, Lynch J, et al. 2004. Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber workers. *J Occup Environ Hyg* 1(6):371-390.
- Madhusree B, Goto S, Ohkubo T, et al. 2002. Mutagenicity testing of 1,3-butadiene, 1,4-pentadiene-3-ol, isoprene, 2,4-hexadiene, cis- and trans-piperlylene. *J Health Sci* 48(1):73-78.
- Malvoisin E, Roberfroid M. 1982. Hepatic microsomal metabolism of 1,3-butadiene. *Xenobiotica* 12(2):137-144.
- Malvoisin E, Lhoest G, Poncelet F, et al. 1979. Identification and quantitation of 1,2-epoxybutene-3 as the primary metabolite of 1,3-butadiene. *J Chromatogr* 178(2):419-425.
- Marshall JD, Granvold PW, Hoats AS, et al. 2006. Inhalation intake of ambient air pollution in California's South Coast Air Basin. *Atmos Environ* 40(23):4381-4392.
- Matanoski GM, Schwartz L. 1987. Mortality of workers in styrene-butadiene polymer production. *J Occup Med* 29(8):675-680.

9. REFERENCES

- Matanoski GM, Santos-Burgoa C, Schwartz L. 1988. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry 1943-1982 (final report prepared under contract to International Institute of Synthetic Rubber Producers, Inc.). Baltimore, MD: The Johns Hopkins University, School of Hygiene and Public Health.
- Matanoski GM, Santos-Burgoa C, Schwartz L. 1990. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ Health Perspect* 86:107-117.
- Matanoski GM, C. S-B, Zeger SL, et al. 1989a. Epidemiologic data related to health effects of 1,3-butadiene. In: Mohn U, ed. *Assessment of inhalation hazards: Integration and extrapolation using diverse data*. New York, NY: Springer-Verlag, 201-214.
- Matanoski GM, Santos-Burgoa C, Zeger SL, et al. 1989b. Nested case-control study of lymphopoietic cancers in workers in the styrene-butadiene polymer manufacturing industry (final report prepared under contract to International Institute of Synthetic Rubber Producers, Inc.). Baltimore, MD: The Johns Hopkins University, School of Hygiene and Public Health.
- Matanoski GM, Schwartz L, Sperrazza J, et al. 1982. Mortality of workers in the styrene-butadiene rubber polymer manufacturing industry. Baltimore, MD: Johns Hopkins University School of Hygiene and Public Health.
- Mayr U, Butsch A, Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. *Toxicology* 74(2-3):135-149.
- MCA. 1974. Chemical safety data sheet SD-55. Properties and essential information for safe handling and use of butadiene. Washington, DC: Manufacturing Chemicals Association.
- McAuliffe C. 1966. Solubility in water of paraffin, cycloparaffin, olefin, acetylene, cycloolefin, and aromatic hydrocarbons. *J Phys Chem* 7(4):1267-1275.
- McCarthy MC, Hafner HR, Montzka SA. 2006. Background concentrations of 18 air toxics for North America. *J Air Waste Manag Assoc* 56(1):3-11.
- McDonald JD, Bechtold WE, Krone JR et al. 2004. Analysis of butadiene urinary metabolites by liquid chromatography-triple quadrupole mass spectrometry. *J Anal Toxicol* 28:168-173.
- McMichael AJ, Spirtas R, Gamble JF, et al. 1976. Mortality among rubber workers: Relationship to specific jobs. *J Occup Med* 18:178-185.
- McMichael AJ, Spirtas R, Kupper LL. 1974. An epidemiologic study of mortality within a cohort of rubber workers, 1964-1972. *J Occup Med* 16:458-464.
- McMichael AJ, Spirtas R, Kupper LL, et al. 1975. Solvent exposure and leukemia among rubber workers: An epidemiologic study. *J Occup Med* 17:234-239.
- McNeal TP, Breder CV. 1987. Headspace gas chromatographic determination of residual 1,3-butadiene in rubber-modified plastics and its migration from plastic containers into selected foods. *J Assoc Off Anal Chem* 70:18-21.

9. REFERENCES

- Meinhardt TJ, Lemen RA, Crandall MS, et al. 1982. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. *Scand J Work Environ Health* 8:250-259.
- Melnick R, Huff J, Miller R. 1989. Toxicology and carcinogenicity of 1,3-butadiene. In: Mohn U, ed. *Assessment of inhalation hazards: Integration and extrapolation using diverse data*. New York, NY: Springer-Verlag, 177-188.
- Melnick RL, Huff J, Chou BJ, et al. 1990a. Carcinogenicity of 1,3-butadiene in C57BL/6 x C3H F₁ mice at low exposure concentrations. *Cancer Res* 50(20):6592-6599.
- Melnick RL, Huff JE, Roycroft JH, et al. 1990b. Inhalation toxicology and carcinogenicity of 1,3-butadiene in B6C3F₁ mice following 65 weeks of exposure. *Environ Health Perspect* 86:27-36.
- Meng Q, Henderson RF, Chen T, et al. 1999. Mutagenicity of 1,3-butadiene at the *Hprt* locus of T-lymphocytes following inhalation exposures of female mice and rats. *Mutat Res* 429(1):107-125.
- Meng Q, Singh N, Heflich RH, et al. 2000. Comparison of the mutations at *Hprt* exon 3 of T-lymphocytes from B6C3F₁ mice and F344 rats exposed by inhalation to 1,3-butadiene or the racemic mixture of 1,2:3,4-diepoxybutane. *Mutat Res* 464(2):169-184.
- Meng Q, Walker DM, McDonald JD, et al. 2007. Age-, gender-, and species-dependent mutagenicity in T cells of mice and rats exposed by inhalation to 1,3-butadiene. *Chem Biol Interact* 166(1-3):121-131.
- Meng Q, Walker DM, Scott BR, et al. 2004. Characterization of *Hprt* mutations in cDNA and genomic DNA of T-cell mutants from control and 1,3-butadiene-exposed male B6C3F₁ mice and F344 rats. *Environ Mol Mutagen* 43(2):75-92.
- Miller LM. 1978. Investigation of selected potential environmental contaminants: Butadiene and its oligomers. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA560278008. PB291684.
- Morrissey RE, Schwetz BA, Hackett PL, et al. 1990. Overview of reproductive and developmental toxicity studies of 1,3-butadiene in rodents. *Environ Health Perspect* 86:79-84.
- Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. *Clin Pharmacokinet* 5(6):485-527.
- NAS/NRC. 1989. Report of the oversight committee. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press. *Biologic markers in reproductive toxicology*.
- Nazaroff WW, Singer BC. 2004. Inhalation of hazardous air pollutants from environmental tobacco smoke in U.S. residences. *J Expo Anal Environ Epidemiol* 14(Suppl 1):S71-S77.
- Nieusma JL, Claffey DJ, Maniglier-Poulet C, et al. 1997. Stereochemical aspects of 1,3-butadiene metabolism and toxicity in rat and mouse liver microsomes and freshly isolated rat hepatocytes. *Chem Res Toxicol* 10:450-456.
- Neligan RE. 1962. Hydrocarbons in the Los Angeles atmosphere. *Arch Environ Health* 5:581-591.
- NIOSH. 1989. National Occupational Exposure Survey (NOES). Cincinnati, OH: U.S. Department of Health and Human Services CfDC, National Institute for Occupational Safety and Health.

9. REFERENCES

- NIOSH. 1994. NIOSH Manual of analytical methods. 1,3-Butadiene. Method 1024. <http://www.cdc.gov/NIOSH/nmam/pdfs/1024.pdf>. June 1, 2009.
- NIOSH. 2005. 1,3-Butadiene. In: NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, <http://www.cdc.gov/niosh/npg/>. May 19, 2009.
- Norppa H, Sorsa M, Vainio H. 1980. Chromosomal aberrations in bone marrow of Chinese hamsters exposed to styrene and ethanol. *Toxicol Lett* 5:241-244.
- NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Research Council. National Academy Press.
- NTP. 1984. NTP toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F₁ mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program.
- NTP. 1993. NTP technical report on the toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F₁ mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 434.
- NTP. 2005. 1,3-Butadiene. In: Report on carcinogens. 11th ed. Research Triangle Park, NC: National Toxicology Program, <http://ntp-server.niehs.nih.gov/ntp/roc/eleventh/profiles/s025buta.pdf>. May 19, 2009.
- NTP. 2011. 1,3-Butadiene. In: Report on carcinogens. 12th edition. U.S. Department of Health and Human Services, National Toxicology Program.
- Oguz O, Karman D, Tuncel G. 2003. Measurement of traffic related toxic air pollutants in an urban atmosphere. *Water Air Soil Pollut Focus*. 3:175-192.
- O'Neil MJ, Heckelman PE, Koch CB, et al. 2006. 1,3-Butadiene. In: O'Neil MJ, Heckelman PE, Koch CB, et al., eds. Merck index. 14th ed. Whitehouse Station, NY: Merck & Co, Inc., 248.
- OSHA. 2009a. 1,3-Butadiene. Occupational Safety & Health Administration. <http://www.osha.gov/dts/sltc/methods/organic/org056/org056.html>. June 2, 2009.
- OSHA. 2009b. Toxic and Hazardous Substances. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1051. <http://www.osha.gov/comp-links.html>. May 29, 2009.
- Osterman-Golkar S, Peltonen K, Anttinen-Klemetti T, et al. 1996. Haemoglobin adducts as biomarkers of occupational exposure to 1,3-butadiene. *Mutagenesis* 11(2):145-149.
- Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.
- Owen PE, Glaister JR. 1990. Inhalation toxicity and carcinogenicity of 1,3-butadiene in Sprague-Dawley rats. *Environ Health Perspect* 86:19-25.

9. REFERENCES

- Owen PE, Glaister JR, Gaunt IF, et al. 1987. Inhalation toxicity studies with 1,3-butadiene 3 two year toxicity/carcinogenicity study in rats. *Am Ind Hyg Assoc J* 48(5):407-413.
- *Pacchierotti F, Tiveron C, Ranaldi R, et al. 1998. Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. *Mutat Res* 397(1):55-66.
- Pankow JF, Luo W, Tavakoli AD, et al. 2004. Delivery levels and behavior of 1,3-butadiene, acrylonitrile, benzene, and other toxic volatile organic compounds in mainstream tobacco smoke from two brands of commercial cigarettes. *Chem Res Toxicol* 17(6):805-813.
- Pankow JF, Watanabe KH, Toccalino PL, et al. 2007. Calculated cancer risks for conventional and "potentially reduced exposure product" cigarettes. *Cancer Epidemiol Biomarkers Prev* 16(3):584-592.
- Patel RN, Hou CT, Laskin AI, et al. 1979. Microbial oxidation of gaseous hydrocarbons. II. Hydroxylation of alkanes and epoxidation of alkenes by cell-free particulate fractions of methane-utilizing bacteria. *J Bacteriol* 139:675-679.
- Patel RN, Hou CT, Laskin AI. 1982a. Oxidation of gaseous hydrocarbons and related compounds by methanotrophic organisms. In: *Developments in industrial microbiology*, Vol. 23, 187-205.
- Patel RN, Hou CT, Laskin AI, et al. 1982b. Microbial oxidation of hydrocarbons: Properties of a soluble methane monooxygenase from a facultative methane utilizing organism *Methlobacterium* sp. strain CRL-26. *Appl Environ Microbiol* 44(5):1130-1137.
- Pellizzari ED, Michael LC, Thomas KW, et al. 1995. Identification of 1,3-butadiene, benzene, and other volatile organics from wok oil emissions. *J Expo Anal Environ Epidemiol* 5(1):77-87.
- Penn A, Snyder CA. 2007. 1,3-Butadiene exposure and cardiovascular disease. *Mutat Res* 621(1-2):42-49.
- Perbellini L, Princivale A, Carpelloni M, et al. 2003. Comparison of breath, blood and urine concentrations in the biomonitoring of environmental exposure to 1,3-butadiene, 2,5-dimethylfuran, and benzene. *Int Arch Occup Environ Health* 76(6):461-466.
- Péry ARR, Bois FY. 2009. Stochasticity in physiologically based kinetics models: Implications for cancer risk assessment. *Risk Anal* 29(8):1182-1191.
- Pohlova H, Rossner P, Sram RJ. 1985. Cytogenetic analysis of human peripheral blood lymphocytes in culture exposed *in vitro* to styrene and styrene oxide. *J Hyg Epidemiol Microbiol Immunol* 29:269-274.
- Preston RJ. 2007. Cancer risk assessment for 1,3-butadiene: Data integration opportunities. *Chem Biol Interact* 166(1-3):150-155.
- Recio L, Osterman-Golkar S, Csanady GA, et al. 1992. Determination of mutagenicity in tissues of transgenic mice following exposure to 1,3-butadiene and N-ethyl-N-nitrosourea. *Toxicol Appl Pharmacol* 117(1):58-64.
- Reiss R. 2006. Temporal trends and weekend-weekday differences for benzene and 1,3-butadiene in Houston, Texas. *Atmos Environ* 40(25):4711-4724.

9. REFERENCES

- Reiss R, Griffin J. 2004. Exploratory data analysis of benzene and 1,3-butadiene measurements for air toxics risk assessment in Houston. Alpharetta, GA: Coordinating Research Council.
- Reynolds P, Von Behren J, Gunier RB, et al. 2003. Childhood cancer incidence rates and hazardous air pollutants in California: An exploratory analysis. *Environ Health Perspect* 111(4):663-668.
- Santos-Burgoa C, Matanoski GM, Zeger S, et al. 1992. Lymphohematopoietic cancer in styrene-butadiene polymerization workers. *Am J Epidemiol* 136(7):843-854.
- Sapkota A, Buckley TJ. 2003. The mobile source effect on curbside 1,3-butadiene, benzene, and particle-bound polycyclic aromatic hydrocarbons assessed at a tollbooth. *J Air Waste Manag Assoc* 53(6):740-748.
- Sapkota A, Halden RU, Dominici F, et al. 2006. Urinary biomarkers of 1,3-butadiene in environmental settings using liquid chromatography isotope dilution tandem mass spectrometry. *Chem Biol Interact* 160(1):70-79.
- Sasiadek M, Jarventaus H, Sorsa M. 1991. Sister-chromatid exchanges induced by 1,3-butadiene and its epoxides in CHO cells. *Mutat Res* 263(1):47-50.
- Sathiakumar N, Delzell E. 2007. A follow-up study of women in the synthetic rubber industry: Study methods. *Chem Biol Interact* 166:25-28.
- Sathiakumar N, Delzell E, Cheng H, et al. 2007. Validation of 1,3-butadiene exposure estimates for workers at a synthetic rubber plant. *Chem Biol Interact* 166(1-3):29-43.
- Sathiakumar N, Graff J, Macaluso M, et al. 2005. An updated study of mortality among North American synthetic rubber industry workers. *Occup Environ Med* 62:822-829.
- Sax SI, Bennett DH, Chillrud SN, et al. 2004. Differences in source emission rates of volatile organic compounds in inner-city residences of New York City and Los Angeles. *J Expo Anal Environ Epidemiol* 14(Suppl 1):S95-S109.
- Schettgen T, Musiol A, Alt A, et al. 2009. A method for the quantification of biomarkers of exposure to acrylonitrile and 1,3-butadiene in human urine by column-switching liquid chromatography-tandem mass spectrometry. *Anal Bioanal Chem* 393(3):969-981.
- Schmidt V, Loeser E. 1985. Species differences in the formation of butadiene monoxide from 1,3-butadiene. *Arch Toxicol* 57:222-225.
- Schmidt V, Loeser E. 1986. Epoxidation of 1,3-butadiene in liver and lung tissue of mouse, rat, monkey and man. *Adv Exp Med Biol* 197:951-957.
- Sielken RL, Jr., Reitz RH, Hays SM. 1996. Using PBPK modeling and comprehensive realism methodology for the quantitative cancer risk assessment of butadiene. *Toxicology* 113(1-3):231-237.
- Sharief Y, Brown AM, Backer LC, et al. 1986. Sister chromatid exchange and chromosome aberration analyses in mice after *in vivo* exposure to acrylonitrile, styrene, or butadiene monoxide. *Environ Mutagen* 8:439-448.

9. REFERENCES

- Shen S, Zhang F, Zeng S, et al. 2009. An approach based on liquid chromatography/electrospray ionization-mass spectrometry to detect diol metabolites as biomarkers of exposure to styrene and 1,3-butadiene. *Anal Biochem* 386(2):186-193.
- Shugaev BB. 1969. Concentrations of hydrocarbons in tissues as a measure of toxicity. *Arch Environ Health* 18:878-882.
- Sigsby JEJ, Tejada S, Ray W. 1987. Volatile organic compound emissions from 46 in-use passenger cars. *Environ Sci Technol* 21:466-475.
- Sills RC, Hong HL, Boorman GA, et al. 2001. Point mutations of K-ras and H-ras genes in forestomach neoplasms from control B6C3F₁ mice and following exposure to 1,3-butadiene, isoprene or chloroprene for up to 2-years. *Chem Biol Interact* 135-136:373-386.
- Slikker W, Andersen ME, Bogdanffy MS, et al. 2004. Dose-dependent transitions in mechanisms of toxicity: Case studies. *Toxicol Appl Pharmacol* 201:226-294.
- Smith TJ, Lin YS, Mezzetti M, et al. 2001. Genetic and dietary factors affecting human metabolism of 1,3-butadiene. *Chem Biol Interact* 135-136:407-428.
- Sorsa M, Osterman-Golkar S, Peltonen K, et al. 1996. Assessment of exposure to butadiene in the process industry [Abstract]. *Toxicology* 113(1-3):77-83.
- Šrám RJ, Rossner P, Peltonen K, et al. 1998. Chromosomal aberrations, sister-chromatid exchanges, cells with high frequency of SCE, micronuclei and comet assay parameters in 1,3-butadiene-exposed workers. *Mutat Res* 419(1-3):145-154.
- SRI. 2008. 1,3-Butadiene. In: 2008 Directory of chemical producers. Menlo Park, CA: SRI Consulting, 457-458.
- Startin JR, Gilbert J. 1984. Single ion monitoring of butadiene in plastics and foods by coupled mass spectrometry — automatic head-space gas chromatography. *J Chromatogr* 294:427-430.
- Stephens ER, Burleson F. 1967. Analysis of the atmosphere for light hydrocarbons. *J Air Pollut Control Assoc* 17:147-153.
- Stephens ER, Burleson FR. 1969. Distribution of light hydrocarbons in ambient air. *J Air Pollut Control Assoc* 19:929-936.
- Stump FD, Dropkin DL. 1985. Gas chromatographic method for quantitative determination of C₂ to C₁₃ hydrocarbons in roadway vehicle emissions. *Anal Chem* 57:2629-2634.
- Stump FD, Tejada S, Ray W, et al. 1989. The influence of ambient temperature on tailpipe emissions from 1984-1987 model year light duty gasoline motor vehicles. *Atmos Environ* 23:307-320.
- Stutz DR, Janusz SJ. 1988. Hazardous materials injuries. A handbook for pre-hospital care 2nd ed. Beltsville, MD: Bradford Communication Corporation, 296-297.

9. REFERENCES

- Sun HN, Wristers JP. 2002. Butadiene. In: Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley & Sons, 365-392.
<http://mrw.interscience.wiley.com/emrw/9780471238966/kirk/article/butasun.a01/current/pdf>. June 2, 2009.
- Sun JD, Dahl AR, Bond JA, et al. 1989a. Metabolism of inhaled butadiene to monkeys: Comparison to rodents. *Exp Pathol* 37:133-135.
- Sun JD, Dahl AR, Bond JA, et al. 1989b. Characterization of hemoglobin adduct formation in mice and rats after administration of [¹⁴C]butadiene or [¹⁴C]isoprene. *Toxicol Appl Pharmacol* 100:86-95.
- Swain CM, Booth ED, Watson WP. 2003. Metabolic distribution of radioactivity in Sprague-Dawley rats and B6C3F₁ mice exposed to 1,3-[2,3-¹⁴C]-butadiene by whole body exposure. *Chem Biol Interact* 145:175-189.
- Sweeney LM, Himmelstein MW, Gargas ML. 2001. Development of a preliminary physiologically based toxicokinetic (PBTk) model for 1,3-butadiene risk assessment. *Chem Biol Interact* 135-136:303-322.
- Sweeney LM, Himmelstein MW, Schlosser PM, et al. 1996. Physiologically based pharmacokinetic modeling of blood and tissue epoxide measurements for butadiene. *Toxicology* 113(1-3):318-321.
- Sweeney LM, Schlosser PM, Medinsky Ma, et al. 1997. Physiologically based pharmacokinetic modeling of 1,3-butadiene, 1,2-epoxy-3-butene, and 1,2:3,4-diepoxymethane toxicokinetics in mice and rats. *Carcinogenesis* 18(4):611-625.
- Swenberg JA, Bordeerat NK, Boysen G, et al. 2011. 1,3-Butadiene: Biomarkers and application to risk assessment. *Chem Biol Interact* 192(1-2):150-154.
- Swenberg JA, Boysen G, Georgieva N, et al. 2007. Future directions in butadiene risk assessment and the role of cross-species internal dosimetry. *Chem Biol Interact* 166(1-3):78-83.
- Tates AD, van Dam FJ, de Zwart FA, et al. 1996. Biological effect monitoring in industrial workers from the Czech Republic exposed to low levels of butadiene [Abstract]. *Toxicology* 113(1-3):91-99.
- Texas Air Control Board. 1990. Written communication to Bill Henriques, Agency for Toxic Substances and Disease Registry, regarding 1,3-butadiene concentrations in air. Texas Air Control Board, Austin, TX.
- Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. *Chemically induced alterations in sexual and functional development: The wildlife/human connection*. Princeton, NJ: Princeton Scientific Publishing, 365-394.
- Thornton-Manning JR, Dahl AR, Bechtold WE, et al. 1995a. Disposition of butadiene monoepoxide and butadiene diepoxide in various tissues of rats and mice following a low-level inhalation exposure to 1,3-butadiene. *Carcinogenesis* 16(8):1723-1731.
- Thornton-Manning JR, Dahl AR, Bechtold WE, et al. 1995b. Gender differences in the metabolism of 1,3-butadiene in Sprague-Dawley rats following a low level inhalation exposure. *Carcinogenesis* 16(11):2875-2878.

9. REFERENCES

Thornton-Manning JR, Dahl AR, Bechtold WE, et al. 1997. Comparison of the disposition of butadiene epoxides in Sprague-Dawley rats and B6C3F₁ mice following a single and repeated exposures to 1,3-butadiene via inhalation. *Toxicology* 123(1-2):125-134.

Thurmond LM, Lauer LD, House RV, et al. 1986. Effect of short-term inhalation exposure to 1,3-butadiene on murine immune functions. *Toxicol Appl Pharmacol* 86(2):170-179.

Thweatt WD, Harward CN, Sr., Parrish ME. 2007. Measurement of acrolein and 1,3-butadiene in a single puff of cigarette smoke using lead-salt tunable diode laser infrared spectroscopy. *Spectrochim Acta A Mol Biomol Spectrosc* 67(1):16-24.

Tice RR. 1988. The cytogenetic evaluation of *in vivo* genotoxic and cytotoxic activity using rodent somatic cells. *Cell Biol Toxicol* 4(4):475-486.

Tice RR, Boucher R, Luke CA, et al. 1987. Comparative cytogenic analysis of bone marrow damage induced in male B6C3F₁ mice by multiple exposures to gaseous 1,3-butadiene. *Environ Mutagen* 9:235-250.

Tommasi AM, de Conti S, Dobrzynska MM, et al. 1998. Evaluation and characterization of micronuclei in early spermatids of mice exposed to 1,3-butadiene. *Mutat Res* 397(1):45-54.

TRI09. 2011. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. <http://www.epa.gov/triexplorer/>. September 28, 2011.

Tsai SP, Ahmed FS, Ransdell JD, et al. 2005. A hematology surveillance study of petrochemical workers exposed to 1,3 butadiene. *J Occup Environ Hyg* 2(10):508-515.

Tsai SP, Wendt JK, Ransdell JD. 2001. A mortality, morbidity, and hematology study of petrochemical employees potentially exposed to 1,3-butadiene monomer. *Chem Biol Interact* 135-136:555-567.

Uusküla M, Järventaus H, Hirvonen A, et al. 1995. Influence of GSTM1 genotype of sister chromatid exchange induction by styrene-7,8-oxide and 1,2-epoxy-3-butene in cultured human lymphocytes. *Carcinogenesis* 16(4):947-950.

Vainiotalo S, Vaananen V, Vaaranrinta R. 2008. Measurement of 16 volatile organic compounds in restaurant air contaminated with environmental tobacco smoke. *Environ Res* 108(3):280-288.

VanGinkel CG, Welten HGJ, Debont JAM. 1987. Oxidation of gaseous and volatile hydrocarbons by selected alkene-utilizing bacteria. *Appl Environ Microbiol* 53:2903-2907.

Victorin K, Stahlberg M. 1988. A method for studying the mutagenicity of some gaseous compounds in *Salmonella typhimurium*. *Environ Mol Mutagen* 11(1):65-77.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. *Eur J Biochem* 238(2):476-483.

Vodicka P, Stetina R, Smerak P, et al. 2006. Micronuclei, DNA single-strand breaks and DNA-repair activity in mice exposed to 1,3-butadiene by inhalation. *Mutat Res* 608(1):49-57.

9. REFERENCES

- Ward EM, Fajen JM, Ruder AM, et al. 1995. Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. *Environ Health Perspect* 103(6):598-603
- Ward JB, Ammenheuser MM, Bechtold WE, et al. 1994. *hprt* Mutant lymphocyte frequencies in workers at a 1,3-butadiene production plant. *Environ Health Perspect* 102(Suppl 9):79-85.
- Ward JB, Ammenheuser MM, Whorton EB, et al. 1996. Biological monitoring for mutagenic effects of occupational exposure to butadiene. *Toxicology* 110:1-7.
- Ward JB, Abdel-Rahman SZ, Henderson RF, et al. 2001. Assessment of butadiene exposure in synthetic rubber manufacturing workers in Texas using frequencies of *hprt* mutant lymphocytes as a biomarker. *Chem Biol Interact* 135-136:465-483.
- Watabe T, Isobe M, Sawahata T, et al. 1978. Metabolism and mutagenicity of styrene. *Scand J Work Environ Health* 4(Suppl 2):142-155.
- Watkinson RJ, Somerville HJ. 1976. The microbial utilization of butadiene. In: Sharpley JM, Kaplan AM, eds., *Proceedings of the Third International Biodegradation Symposium* London: Applied Science Publishers, 35-42.
- West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. *J Pediatr* 32:10-18.
- Whitworth KW, Symanski E, Coker AL. 2008. Childhood lymphohematopoietic cancer incidence and hazardous air pollutants in Southeast Texas, 1995-2004. *Environ Health Perspect* 116:1576-1580.
- WHO. 2000. Air quality guidelines. 2nd edition. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/air/activities/20050223_4. May 11, 2009.
- WHO. 2006. Guidelines for drinking-water quality. 3rd edition. Geneva, Switzerland: World Health Organization. http://www.who.int/water_sanitation_health/dwq/gdwq3/en/. May 11, 2009.
- Wickliffe JK, Ammenheuser MM, Adler PJ, et al. 2009. Evaluation of frequencies of *HPRT* mutant lymphocytes in butadiene polymer workers in a southeast Texas facility. *Environ Mol Mutagen* 50(2):82-87.
- Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. *Mineral metabolism: An advance treatise. Volume II: The elements Part A*. New York, NY: Academic Press, 1-247.
- Wilson RH. 1944. Health hazards encountered in the manufacture of synthetic rubber. *J Am Med Assoc* 124(11):701-703.
- Xiao Y, Tate AD. 1995. Clastogenic effects of 1,3-butadiene and its metabolites 1,2-epoxybutene and 1,2,3,4-diepoxybutane in splenocytes and germ cells of rats and mice *in vivo*. *Environ Mol Mutagen* 26(2):97-108.
- Zhao C, Vodicka P, Sram RJ, et al. 2000. Human DNA adducts of 1,3-butadiene, an important environmental carcinogen. *Carcinogenesis* 21(1):107-111.

9. REFERENCES

Zhao C, Vodicka P, Sram RJ, et al. 2001. DNA adducts of 1,3-butadiene in humans: Relationships to exposure, GST genotypes, single-strand breaks, and cytogenetic end points. *Environ Mol Mutagen* 37(3):226-230.

Zhou XT, Li LR, Cui MY, et al. 1986. Cytogenetic monitoring of petrochemical workers [Abstract]. *Mutat Res* 175(4):237-242.

Zhuang SM, Cochran C, Goodrow T, et al. 1997. Genetic alterations of p53 and ras genes in 1,3-butadiene- and 2',3'-dideoxycytidine-induced lymphomas. *Cancer Res* 57(13):2710-2714.

Zhuang SM, Wiseman RW, Soderkvist P. 2002. Frequent mutations of the *Trp53*, *Hras1* and β -catenin (*Catnb*) genes in 1,3-butadiene-induced mammary adenocarcinomas in B6C3F₁ mice. *Oncogene* 21(36):5643-5648.

Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. *Pediatr Res* 12(1):29-34.

9. REFERENCES

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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 (K_d)—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.

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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.

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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₎ (LC₅₀)—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₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—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.

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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

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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 $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

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

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

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

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

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

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

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

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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₎ (TD₅₀)—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

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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.

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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.

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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").

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- (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/m³ 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.

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- (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

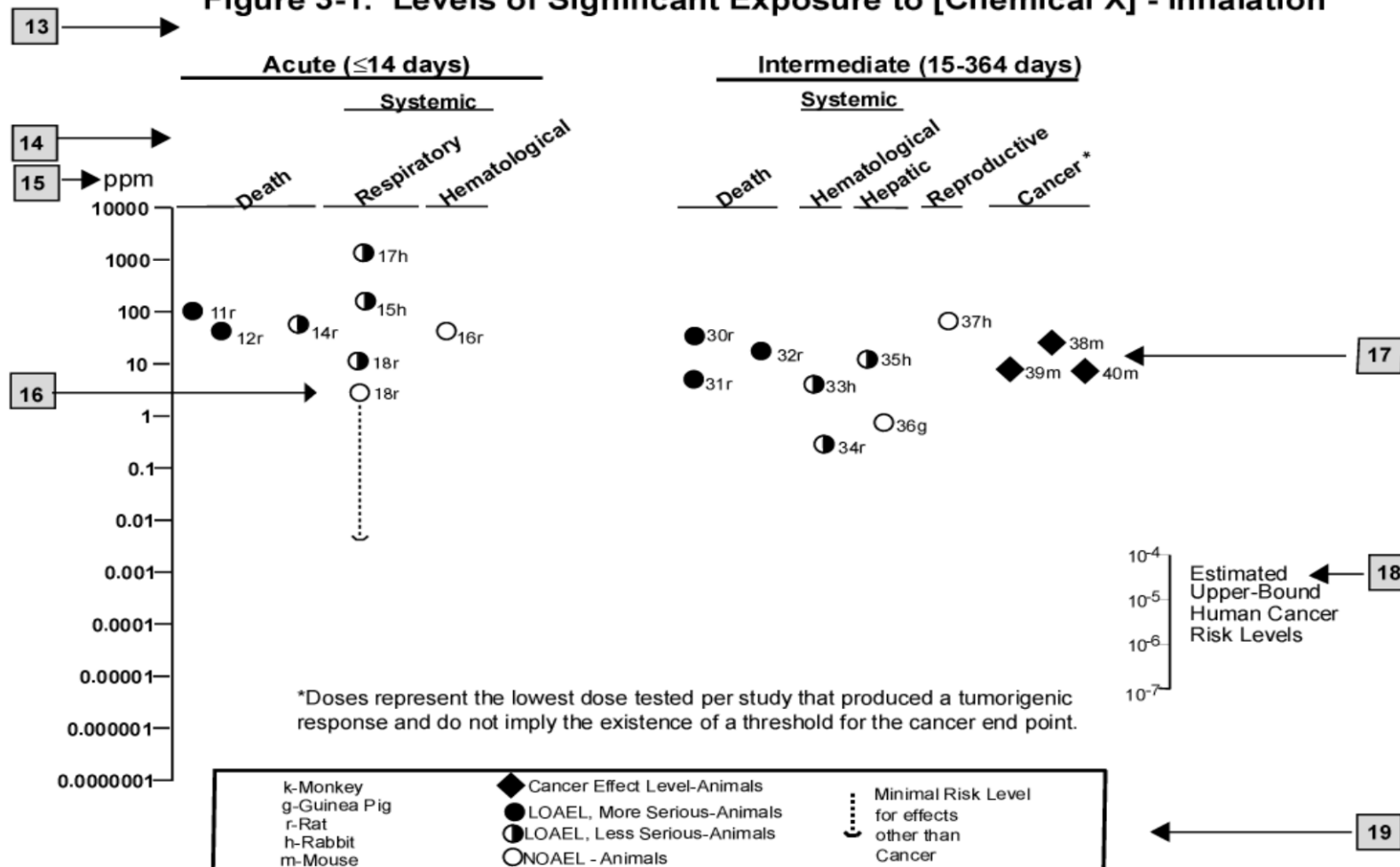
| | Key to figure ^a | Species | Exposure frequency/ duration | System | NOAEL (ppm) | LOAEL (effect) | | Reference |
|---|----------------------------|-----------------------|---------------------------------|-------------------------------|-------------|--------------------|--------------------------------------|----------------------|
| | | | | | | Less serious (ppm) | Serious (ppm) | |
| 2 | → | INTERMEDIATE EXPOSURE | | | | | | |
| | | 5 | 6 | 7 | 8 | 9 | | 10 |
| 3 | → | Systemic | ↓ | ↓ | ↓ | ↓ | | ↓ |
| 4 | → | 18 | Rat | 13 wk 5 d/wk 6 hr/d | Resp | 3 ^b | 10 (hyperplasia) | Nitschke et al. 1981 |
| | | 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 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

APPENDIX C

| | |
|------------------|---|
| DOT | Department of Transportation |
| DOT/UN/ | Department of Transportation/United Nations/ |
| NA/IMDG | 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 |
| K _d | 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 | lutinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Levels of Significant Exposure |
| LT ₅₀ | lethal time, 50% kill |
| m | meter |
| MA | <i>trans,trans</i> -muconic acid |
| MAL | maximum allowable level |
| mCi | millicurie |

APPENDIX C

| | |
|----------|--|
| 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 |

APPENDIX C

| | |
|------------------|--|
| 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 |

APPENDIX C

| | |
|---------------|--------------------------|
| $>$ | greater than |
| \geq | greater than or equal to |
| $=$ | equal to |
| $<$ | less than |
| \leq | 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 |

APPENDIX C

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APPENDIX D. INDEX

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APPENDIX D

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1,3-Butadiene

| | |
|---|---|
| MAK value | – |
| Peak limitation | – |
| Absorption through the skin | – |
| Sensitization | – |
| Carcinogenicity (1998) | Category 1 |
| Prenatal toxicity | – |
| Germ cell mutagenicity (1998) | Germ cell mutagen group 2 |
| BAT value | – |
| Synonyms | bivinyll α,γ -butadiene divinyll erythrene vinylethylene biethylene pyrrolylene |
| Chemical name (CAS) | 1,3-butadiene |
| CAS number | 106-99-0 |
| Structural formula | $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$ |
| Molecular formula | C_4H_6 |
| Molecular weight | 54.09 |
| Melting point | –108.9°C |
| Boiling point | –4.5°C |
| Vapour pressure at 20°C | 2477 hPa |
| 1 ml/m³ (ppm) \cong 2.244 mg/m³ | 1 mg/m³ \cong 0.445 ml/m³ (ppm) |

1 Toxic Effects and Mode of Action

The acute toxicity of 1,3-butadiene is very low. The oral LD₅₀ values are 5480 mg/kg body weight for the rat and 3210 mg/kg body weight for the mouse (NIOSH 1979). Repeated exposure of animals to concentrations up to 6700 ml/m³ did not produce pathological symptoms. Narcotic effects do not appear until the exposure concentrations are very high; the narcotic concentration range is not better specified in the literature (Carpenter *et al.* 1944).

In a 2-year carcinogenicity study with rats, unspecific symptoms such as increased discharge from the eyes and nose and “mild ataxia” were seen after exposure of rats for 6 hours daily to a 1,3-butadiene concentration of 8000 ml/m³ (Crouch *et al.* 1979a, 1979b). In a group of animals exposed in parallel to 1000 ml/m³, such symptoms were not observed.

1,3-Butadiene or its epoxides are mutagenic *in vivo*. 1,3-Butadiene is carcinogenic in the rat and mouse and is a germ cell mutagen. In workers exposed to 1,3-butadiene, the incidence of lymphosarcomas was increased.

2 Metabolism and Metabolic Activation

Microsomal monooxygenases convert 1,3-butadiene to its reactive monoepoxide, 1,2-epoxy-3-butene, which was identified by gas chromatography and mass spectroscopy in incubations of 1,3-butadiene with liver microsomes and NADPH *in vitro* by Malvoisin *et al.* (1979). More extensive studies (Bolt *et al.* 1983) demonstrated that both optical isomers of 1,2-epoxy-3-butene (R and S) are produced in this process. These isomers are then subject to further metabolism (Malvoisin *et al.* 1982, Malvoisin and Roberfroid 1982) probably involving the enzymes epoxide hydrolase (Malvoisin *et al.* 1982), monooxygenase (Malvoisin and Roberfroid 1982) and glutathione-S-transferase (Bolt *et al.* 1983). Conceivable metabolites include 3-butene-1,2-diol (Malvoisin *et al.* 1982), 3,4-epoxy-1,2-butanediol (Malvoisin and Roberfroid 1982), the very reactive diepoxide of 1,3-butadiene (Malvoisin and Roberfroid 1982) and glutathione conjugates (Bolt *et al.* 1983, Malvoisin and Roberfroid 1982). This concept is in agreement with early reports that erythritol (1,2,3,4-butanetetrol) is excreted in the urine by various species of animal after exposure to 1,3-butadiene (Carpenter *et al.* 1944).

In vivo metabolic and pharmacokinetic studies (Bolt *et al.* 1983) have been carried out with rats in closed “dessicator” systems and demonstrate that during exposure to concentrations up to 1000 ml/m³, the metabolism of 1,3-butadiene is rapid and obeys first order kinetics. At concentrations above 1000 ml/m³, transition to “non-linear kinetics” is observed as the metabolizing enzymes become saturated. In closed systems the epoxide metabolite, 1,2-epoxy-3-butene, can be detected directly in the gas phase. Thus this epoxide is formed from 1,3-butadiene not only *in vitro* but also under *in vivo* exposure conditions.

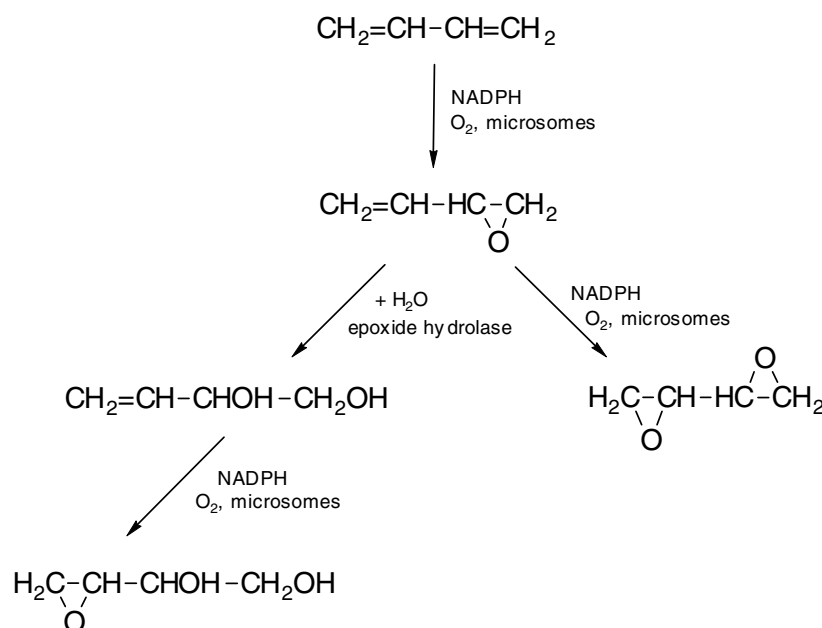


Figure 1. Metabolism of 1,3-butadiene *in vitro* with rat liver microsomes (from Malvoisin and Roberfroid 1982)

2.1 Haemoglobin adducts at the *N*-terminal valine

2.1.1 Adducts of the monoepoxide of 1,3-butadiene

Male B6C3F₁ mice and SD rats were exposed to 1,3-butadiene concentrations of 2, 10 or 100 ml/m³, 6 hours daily, 5 days per week for 4 weeks. The concentrations of the adduct *N*-(2-hydroxy-3-butenyl)valine found for the three exposure concentrations were 100, 375 and 3800 pmol/g haemoglobin for mice and 50, 250 and 875 pmol/g haemoglobin for rats (Osterman-Golkar *et al.* 1993).

When Wistar rats were exposed to 1,3-butadiene concentrations of 250, 500 and 1000 ml/m³, 6 hours/day, 5 days/week for 2 weeks, the levels of *N*-(2-hydroxy-3-butenyl)valine found were 500, 1500 and 3000 pmol/g haemoglobin (Osterman-Golkar *et al.* 1991).

In rats and mice exposed to 1,3-butadiene concentrations between 50 and 1300 ml/m³, 6 hours/day for 5 days, the concentration of *N*-(2-hydroxy-3-butenyl)valine in haemoglobin at the end of exposure increased with the exposure concentration. For mice the concentration-effect curve became flatter above 500 ml/m³. The adduct concentrations found after the 500 ml/m³ exposure were 3.5 nmol/g haemoglobin for rats and 17 nmol/g haemoglobin for mice (Albrecht *et al.* 1993).

In the blood of male Wistar rats exposed to 500 ml/m³, 6 hours/day for 5 days, the level of *N*-(2-hydroxy-3-butenyl)valine found in haemoglobin was 4.7 pmol/g (Elovaara *et al.* 1994).

In non-smoking workers exposed to 1,3-butadiene at concentrations which were probably in the range from under 1 to 3.5 ml/m³ (concentrations not determined during the study), the levels of *N*-(2-hydroxy-3-butenyl)valine found in haemoglobin were 1.1 to 2.6 pmol/g. The values for control persons who were not employed in the production process and were exposed to 0.03 ml/m³ were below the detection limit of 0.5 pmol/g haemoglobin (Osterman-Golkar *et al.* 1993).

The levels of this adduct in workers exposed to concentrations less than 1 ml/m³ were below 0.5 pmol/g haemoglobin and in those exposed to concentrations below 3 ml/m³ about 0.5 pmol/g (Sorsa *et al.* 1996).

In workers exposed to 1,3-butadiene levels of less than 1 ml/m³, the concentrations of *N*-(2-hydroxy-3-butenyl)valine in blood were in the range from below 1 to below 4 pmol per g haemoglobin and in control persons were always in the range from below the detection limit of 1 pmol/g to 8 pmol/g haemoglobin (van Sittert and van Vliet 1994).

This haemoglobin adduct was also detected in workers exposed to 1,3-butadiene concentrations of 11.2 ± 18.6 mg/m³ (5.0 ± 8.3 ml/m³) at a level of 0.16 ± 0.099 pmol/g. In persons exposed to 1,3-butadiene concentrations below 1.2 mg/m³ (0.5 ml/m³), the level was about 0.05 pmol/g haemoglobin (Osterman-Golkar *et al.* 1996).

2.1.2 Adducts of the diepoxide of 1,3-butadiene

In two workers who were exposed to concentrations of 1,3-butadiene below 3 ml/m³, the level of *N*-(2,3,4-trihydroxybutyl)valine in haemoglobin was five times that in two non-exposed persons. The concentration of the diepoxide adducts was about 70 times that of the monoepoxide adducts. However, in rats exposed to 50, 200 or 500 ml/m³, the adduct concentration after the 500 ml/m³ exposure was the same as that found after the 50 ml/m³ exposure. The ratio of diepoxide adducts to monoepoxide adducts varied between 4 and 26. The difference between the species man and rat in the quantity of diepoxide adducts was thus smaller than for the monoepoxide adducts. The haemoglobin binding index after intraperitoneal injection into rats of epoxybutanediol or the diepoxide of 1,3-butadiene was similar to that of ethylene oxide. After inhalation exposure the haemoglobin binding index was a factor of 10 smaller than after i.p. injection (Pérez *et al.* 1997).

2.2 Biological effect-monitoring

In 17 male and female persons (how many of each sex not specified) who had been exposed for 7.2 ± 5.6 years to 1,3-butadiene concentrations of 1–3 ml/m³ (about 72 % of the assayed values were below 1 ml/m³) and aged on average 34.5 years (controls 40.7 years), no increase in the incidence of chromosomal aberrations (without gaps), sister chromatid exchange (SCE) or micronuclei in lymphocytes could be detected. The same result was obtained with 23 male workers who had been employed in another factory for 15.3 ± 10.5 years and were on average 37.8 years old (controls 38.1 years). The assayed exposure levels were 1.8 ± 2.8 ml/m³ (43 % of the values were below 1 ml/m³). The proportion of smokers in the collectives was not specified. The factor “smoking” was

correlated with the incidence of SCE and micronuclei, the factor “age” with the presence of chromosomal aberrations and micronuclei, the factor “sex” with the incidence of micronuclei (Sorsa *et al.* 1994).

The exposed persons and controls examined in the study by Sorsa *et al.* (1994) together with another 16 exposed and 20 control persons were characterized with respect to their glutathione transferase genotypes. The data for 53 exposed persons and 46 controls were reported: the incidence of chromosomal aberrations (without gaps) was significantly increased in the lymphocytes of workers without the gene for glutathione transferase theta-1 ($n = 9$) who were exposed to 1,3-butadiene. The incidence of aberrations was $3.8 \pm 0.8\%$ (controls $2.5 \pm 0.7\%$, $n = 8$). In exposed persons with the gene ($n = 44$), the incidence of aberrations was $2.0 \pm 0.2\%$ (controls $2.0 \pm 0.2\%$, $n = 38$). For the incidences of SCE and micronucleus formation, however, no differences were detected. The average exposure concentrations were below 3 ml/m^3 but peak 1,3-butadiene levels of more than 100 ml/m^3 were also measured (Sorsa *et al.* 1996).

In the lymphocytes of 10 non-smokers (9 male and 1 female) who had been exposed to 1,3-butadiene for 6 ± 9.6 years and were on average 40.8 years old (controls: 8 male and 2 female non-smokers, average age 40.1 years, exposed to 1,3-butadiene concentrations of 0.03 ml/m^3), the sum of all chromosomal aberrations was not significantly increased. The average 1,3-butadiene concentration in the factory was given as 3.5 ml/m^3 ; however, most persons were exposed to 1 ml/m^3 . The actual exposure levels for the persons who were examined are unclear. In persons exposed to higher levels, determined from the level of butadiene metabolites in urine, there was an increased incidence of dicentric chromosomes. After irradiation of the lymphocyte cultures with gamma rays, the proportion of cells with chromosomal aberrations was significantly increased. The authors ascribe this result to a deficiency of DNA repair in the lymphocytes from the exposed persons (Au *et al.* 1995).

The lymphocytes of the same persons were examined for mutations at the HPRT (hypoxanthine guanine phosphoribosyl transferase) locus by an autoradiographic method in the studies of Legator *et al.* (1993) and Ward *et al.* (1994). The incidence of mutations was significantly increased in the exposed persons and correlated with the levels of the butadiene metabolite 1,2-dihydroxy-4-(*N*-acetylcysteinyl-*S*)butane in the urine. The incidence of mutations in persons exposed to 0.03 ml/m^3 was not increased above that in non-exposed persons.

An update of this study which was carried out after the exposure levels in the factory had been reduced revealed a significantly increased incidence of HPRT mutations in the lymphocytes of 7 persons said to have high-level exposure ($0.30 \pm 0.59 \text{ ml/m}^3$) compared with that in 15 persons exposed to 0.21 ± 0.21 or $0.12 \pm 0.27 \text{ ml/m}^3$. The metabolite concentrations in the urine of the group of persons classified as having high-level exposure were not significantly higher than those in the two other groups. In another factory in which styrene-butadiene synthetic rubber was produced, the incidence of HPRT mutations was increased in the lymphocytes of smokers and non-smokers exposed to butadiene levels between 0.25 and 1 ml/m^3 . Smoking also increased the incidence of HPRT mutants (Ward *et al.* 1996).

The lymphocytes of 19 persons exposed to 1,3-butadiene were examined for HPRT mutations (T cell cloning efficiency), chromosomal aberrations and DNA strand breaks

(COMET assay). The butadiene concentrations determined after personal sampling on the day on which the blood samples were taken were in the range between 0.012 and 19.77 ml/m³ with an average level of 1.76 ± 4.20 ml/m³. A control group standardized for the factors “age” and “smoking” was included. The incidences of HPRT mutations and DNA strand breaks were not increased, that of micronuclei slightly but not significantly increased. The factor “smoking” also had no effect on the incidence of mutations. The proportion of lymphocytes with chromosomal aberrations (without gaps) was significantly increased in the exposed persons (3.11 ± 1.33 % compared with 2.03 ± 1.53 %) (Tates *et al.* 1996).

In 18 female and 14 male workers who had been exposed to 1,3-butadiene for an average of 6.5 and 8.6 years, the incidence of HPRT mutations determined in a test for T cell cloning efficiency was not significantly increased. The exposure levels determined in the various working areas were 1.0, 1.1 and 3.5 ml/m³ and during maintenance work 45 ml/m³. About 80 % of the male workers were smokers; a control group standardized for smoking was included (Hayes *et al.* 1996).

In summary, the studies of HPRT mutations in the lymphocytes of persons exposed to 1,3-butadiene have yielded contradictory results which can perhaps be explained by differences in exposure levels and detection methods (Himmelstein *et al.* 1997, Pacchierotti *et al.* 1998). In the studies of Legator *et al.* (1993) and Ward *et al.* (1994) the incidence of HPRT mutations correlated with the level of 1,3-butadiene metabolites excreted in the urine. In the lymphocytes of persons exposed to 1,3-butadiene, the incidence of chromosomal aberrations was increased and associated with the absence of the glutathione transferase theta-1 gene. Chromosomal aberrations are a more sensitive end-point than HPRT mutations because the target is the whole genome whereas the mutagenicity test detects only one single affected gene (Tates *et al.* 1996). Likewise, in animal studies the clastogenic effect of butadiene was more readily detected than the mutations at the HPRT locus (Pacchierotti *et al.* 1998).

3 Effects in Man

Of the more recent studies, especially that by Delzell *et al.* (1996), in which employees in synthetic rubber production (styrene-butadiene synthetic rubber) were investigated, and that by Divine and Hartmann (1996) of the persons employed in the production of monomeric 1,3-butadiene are of importance. In addition to these very informative studies, both in respect of size and observation period, there is another study of the production of 1,3-butadiene monomer which is relevant for the evaluation (Ward *et al.* 1995). There are also three less extensive studies (Bond *et al.* 1992, Cowles *et al.* 1994, Downs *et al.* 1993) which provide less information.

All the available information has already been reviewed and evaluated by other bodies (ECETOC 1997, Himmelstein *et al.* 1997). In these two publications the individual studies are described in detail. Therefore the epidemiological studies are presented only briefly here.

3.1 1,3-Butadiene synthetic rubber production

3.1.1 Delzell *et al.* (1996)

Some of the employees included in this study had already taken part in other studies (Matanoski *et al.* 1990, Meinhardt *et al.* 1982). Therefore the present document discusses only the results of the study by Delzell *et al.* (1996). In this study, the mortality of 15649 men who had been employed for at least one year in one of eight factories producing synthetic rubber was investigated; 75 % of the employees were exposed to 1,3-butadiene. During the observation period from 1943 until 1991, a total of 3976 persons died, and for 101 of these the cause of death was given as malignant neoplasm of the lymphatic and haematopoietic tissue (International Classification of Diseases, ICD-9: 200–208). This number corresponds approximately with the expected number of 93.4 such cases (standardized mortality ratio, SMR = 108), calculated from the mortality data for USA or Ontario (for the Canadian employees).

Further differentiation reveals that among the 101 cases, lymphosarcoma (ICD-9: 200) was given as the cause of death in 11 cases (SMR = 80), leukaemia (ICD-9: 204–207) in 48 cases (SMR = 131, $p < 0.05$) and other lymphatic disorders in the remaining 42 cases (SMR = 97).

Of particular interest is the cause of death “leukaemia”. The data were subdivided according to criteria such as duration, date of beginning and kind of employment. This analysis demonstrated that the leukaemia risk was increased most for workers who had been employed for at least 10 years and observed for more than 20 years; 28 of the 48 cases of leukaemia belonged to this group (SMR = 224, $p < 0.05$). The risk was particularly high for black workers (SMR = 436, 7 cases). The risk was also increased for persons who began work after 1950 (beginning 1950–1959: 20 cases, SMR = 200; beginning after 1960: 8 cases observed, SMR = 150). For persons who began this work before 1950, an SMR of 104 was observed (17 cases). The increased risk was concentrated among persons who worked in the laboratory (10 cases, SMR = 431), in maintenance (13 cases, SMR = 265), in polymerisation (15 cases, SMR = 250) and in coagulation (7 cases, SMR = 248).

For the period after 1970 the leukaemia risk can be further differentiated on the basis of the official statistics of the USA. After 1970 a total of 35 persons died from leukaemia (SMR = 178, $p < 0.05$); for 20 of the 35, chronic leukaemia was given as the cause of death (SMR = 241, $p < 0.05$) and for 15, acute leukaemia (SMR = 132).

In the 1940s the exposure levels averaged about 6 ml/m³; in the subsequent decades they were continually reduced (1950–1959: 5 ml/m³; 1960–1969: 3 ml/m³; 1970–1979: 2 ml/m³; 1980–1989: 1 ml/m³; after 1990: 0.8 ml/m³). For certain workplaces average levels of 29 ml/m³ with peak values up to 10000 ml/m³ were given (Macaluso *et al.* 1996).

In a further analysis of this study, the dose-response relationship between exposure to 1,3-butadiene and the development of leukaemia was investigated (Macaluso *et al.* 1996). Evaluated were data for a total of 16610 workers of whom 58 died from leukaemia. The risk increased significantly with the 1,3-butadiene exposure ($p < 0.01$). The

exposure (in ml/m^3 -years) was subdivided into 5 classes (0, < 1, 1–19, 20–79, ≥ 80). The number of deaths in the individual classes varied between 4 and 18. The SMR value for the non-exposed persons was 76. In the lowest exposure class the SMR was 41 and it increased steadily with increasing exposure (SMR = 133, 166 and 264). The authors interpreted their results to mean that exposure to 1,3-butadiene causes a dose-dependent increase in the incidence of leukaemia. Such a significant increase in risk is not seen in the analysis of exposure to styrene.

3.1.2 Bond *et al.* (1992)

In this study of 420 workers who were employed in the processing of styrene-butadiene-latex, for 13 employees the cause of death was a tumour. In one case leukaemia was given as the cause of death (expected number = 0.9). The expected total number of malignant neoplasms of the lymphatic system was 2.2 cases.

3.1.3 Downs *et al.* (1993)

In an abstract, data are reported for the mortality of 1037 workers who were exposed to acrylonitrile-butadiene-styrene. For two workers the cause of death was given as leukaemia or a related disease; the expected number of cases was 2.8.

3.2 Production of 1,3-butadiene

3.2.1 Divine and Hartmann (1996)

This publication describes data for the mortality of 2795 workers who were employed for at least 6 months between 1942 and 1994 in a factory producing 1,3-butadiene. By the end of 1994, a total of 1222 employees had died (SMR = 88). In 42 cases the cause of death was given as “malignant neoplasms of the lymphatic and haematopoietic tissue” (SMR = 147, $p < 0.05$). The incidence of lymphosarcomas was increased; this cause of death was given for 9 employees (SMR = 191). The number of observed deaths from leukaemia was approximately the expected number (13 observed, 11.5 expected cases: SMR = 113).

Analysis of the data for the 9 employees who died from a lymphosarcoma revealed that 6 of them had been employed for less than 5 years (SMR = 261) and 7 of the 9 workers had begun work in the factory before 1946 (SMR = 241).

The differentiation of the 42 persons who had died from malignant neoplasms of the lymphatic and haematopoietic tissues revealed that the risk was highest among workers employed for less than 5 years (22 cases, SMR = 162, $p < 0.05$). For a duration of employment between 5 and 19 years, the SMR was reduced to 135 (8 cases). For workers who had been employed for 20 years and more, the observed risk was similar (12 cases,

SMR = 132), for those employed for less than 5 years, the SMR for leukaemia was 147 (8 cases).

The analysis of the effect of period of employment on lymphosarcoma risk is not straightforward because about half of the workers were employed for less than 5 years (1390 of the 2795 workers). The numbers of cases in the various subgroups are too small to identify any increase in the lymphosarcoma risk with sufficient certainty. For example, the statistical power of these data to demonstrate an SMR of 200 or more for the workers employed for longer than 5 years (3 observed against 2.4 expected cases) is just 35%. Similar values apply for the subgroups with beginning of employment after 1946 or with low exposure levels. Thus the lack of significant effects cannot be interpreted as lack of effects.

Differentiation according to date of the beginning of exposure shows an increased lymphosarcoma risk for workers who began work before 1946 (7 cases, SMR = 241). On the other hand, workers who were first exposed between 1946 and 1949 have an increased risk of developing leukaemia (6 cases, SMR = 195) and other lymphatic tumours (6 cases, SMR = 200).

The authors make no statement as to the absolute exposure levels. In the publication, however, relative levels of exposure are given. As basis the time from 1986–1994 was used. For the period before 1986 the following factors were given: 1977–1985: exposure factor 2; 1960–1976: factor 4; 1946–1959: factor 8; before 1946: factor 10 and higher. On the basis of these factors and the kind of workplace, the employees were subdivided into three exposure classes (with increasing exposure: “background”, “low”, “varied”). The mortality risk for all causes of death was similar in the two exposed classes (SMR = 87 and SMR = 86). For the cause of death “lymphosarcoma” a dose-response relationship was seen (background: SMR = 0, low: SMR = 109, varied: SMR = 249).

3.2.2 Ward *et al.* (1995)

The mortality of 364 workers who were exposed to 1,3-butadiene in the years between 1940 and 1979 was investigated in this study. By the end of 1990, a total of 185 of the workers had died (SMR = 91). For 7 of them, malignant neoplasms of the lymphatic and haematopoietic tissue were the cause of death (SMR = 175). For 4 of these 7 employees, lymphosarcoma was given as the cause of death (SMR = 577, $p < 0.05$); two others died from leukaemia (SMR = 123). For three of the four persons who died from lymphosarcoma, the latency period was more than 30 years. In the group of persons with a latency period of more than 30 years, the SMR was increased to 1080 (95% CI: 220–3160). Three of the four persons who died from lymphosarcoma had been employed for less than 5 years. These three persons were all first exposed in 1946 or earlier.

3.2.3 Cowles *et al.* (1994)

In this study, the mortality of 614 workers who had been employed and exposed to 1,3-butadiene in a petrochemical plant between 1948 and 1989 was analysed. A total of 24 workers had died, four of them with a tumour, none with leukaemia or related causes

of death. The study has only limited power because of the low numbers of expected cases.

3.3 Evaluation

3.3.1 1,3-Butadiene synthetic rubber production

The less extensive studies by Bond *et al.* (1982) and Downs *et al.* (1993) detected no increases in tumour-related mortality. The study of about 16000 employees by Delzell *et al.* (1996) revealed an increased risk for leukaemia but not for lymphosarcoma. The leukaemia risk increased with increasing exposure levels and was observed especially in workers with a latency period of more than 20 years. An increased risk of developing leukaemia is most readily seen in workers who were first exposed after 1950. In the mid 1950s the process was changed from hot to cold polymerisation. This change could provide an explanation for the increased risk for workers first exposed after 1950. The authors commented on the different risks in the different workplaces and wrote that the workers with a high leukaemia risk who worked in the laboratory were exposed to high levels of 1,3-butadiene but to low or moderate levels of styrene. In other workplaces associated with increased risk, there were high levels of exposure to both 1,3-butadiene and styrene. In the low risk workplaces, the 1,3-butadiene exposure levels were low. Also noteworthy is the increase in the leukaemia risk as a function of the cumulative exposure to 1,3-butadiene, but not as a function of styrene exposure. However, the fact that the risk for workers who were first exposed before 1950 was not increased although the exposure levels were highest at that time is evidence against a dose-response relationship. In this context, the authors point out that they were unable to identify all the workers who had already finished working in the synthetic rubber production process before 1950. To what extent the incompleteness of this data affects the results is unclear.

3.3.2 1,3-Butadiene production

Three different studies have analysed the risks for workers in 1,3-butadiene production (Cowles *et al.* 1994, Divine and Hartmann 1996, Ward *et al.* 1995). Since in the study by Cowles *et al.* (1994) the beginning of employment for most of the workers was after the year 1970 and thus the latency period is too short for an evaluation, this study is not included in the present evaluation.

Both of the other two studies found an increased risk of dying from a lymphosarcoma. The overall SMR is 241 (95 % confidence interval (CI): 128–414). The risk is especially increased for workers who were first exposed before 1946.

In the more extensive study by Divine and Hartmann (1996), no relationship between the duration of employment and the risk can be demonstrated. The highest risk was seen in workers who had been employed for less than five years. The duration of exposure or of employment at a particular workplace is frequently used as a substitute for the level of

exposure. This assumption is, however, often not justified, especially in situations where high levels of exposure result in the worker leaving the workplace at an early date (Landrigan 1993, Steenland *et al.* 1996).

In this study, it is striking that about half of the workers were employed in 1,3-butadiene production for less than 5 years. The amount of 1,3-butadiene produced was reduced markedly after the end of World War II. The authors draw attention to this fact and suggest that exposure at other workplaces contributed to the increased risk. This hypothesis is not discussed in any detail. It does not, however, seem very plausible that a large proportion of these workers was exposed at other workplaces to a substance which caused the increased risk but remained unidentified. The two studies are in agreement that the workers with an increased risk are in the subgroup who were employed before 1946 when the exposure levels were very high.

For workers exposed during production of 1,3-butadiene, an increased leukaemia risk cannot be demonstrated.

3.3.3 Summary of all the study results

Employment in the production of styrene-butadiene synthetic rubber is associated with an increased leukaemia risk especially for workers employed during the period between 1950 and 1959 (SMR = 200). The risk increases with increasing levels of exposure to 1,3-butadiene. No increased lymphosarcoma risk can be detected. Employment in the production of 1,3-butadiene, however, is associated with an increased lymphosarcoma risk, but no increase in the leukaemia risk can be detected (Table 1).

Some authors put this difference down to diagnostic imprecision (e.g. Landrigan 1993). The classification of some subgroups of leukaemia and lymphosarcoma in the ICD-system does seem to be problematical (Peschel 1997). Overlap, especially between chronic lymphatic leukaemia and lymphosarcoma, does seem possible. In the workers employed in the production of 1,3-butadiene synthetic rubber, an increased incidence of chronic lymphatic leukaemia is observed, but these conceivable differentiation difficulties are insufficient to account for the different results obtained from the two exposure situations. Presumably other workplace conditions are responsible for the difference in tumour localization.

In both studies of the effects of monomeric 1,3-butadiene, an increased lymphosarcoma risk is demonstrated. In employees in the production of styrene-butadiene synthetic rubber there is an increased risk of developing leukaemia. However, further analysis is required to determine which substance is responsible for the risk in each case. The demonstrated dose-response relationship is evidence for 1,3-butadiene. The difference in localization is evidence against the effects being caused by this substance.

Taking all the results together, however, 1,3-butadiene must be classified as a human carcinogen.

Table 1. Numbers of deaths and SMR for cases of cancer of the lymphatic and haematopoietic system (LHC) among employees in the production of styrene-butadiene synthetic rubber and in the production of 1,3-butadiene monomer

| Literature reference cohort | Exposure | Leukaemia ^a [SMR (95% CI)] | Lymphosarcoma ^a [SMR (95% CI)] | Other LHC ^a [SMR (95% CI)] | All LHC ^a [SMR (95% CI)] |
|---|---|--|--|--|--|
| Delzell <i>et al.</i> (1996) 15649 employees in synthetic rubber production | 1943–1991 whole cohort | 48/36.6 [131 (97–174)] | 11/13.7 [80 (40–144)] | 42/43.1 [97 (70–132)] | 101/93.4 [108 (88–131)] |
| | employed for >10 years | 28/n.s. [224 (149–323)] ^b | | | |
| | beginning 1950–1959 | 20/10.0 [200 (122–310)] ^b | | | |
| | beginning before 1959 | 8/6 [150 (65–296)] | | | |
| | workplace: | | | | |
| | laboratory | 10/n.s. [431 (207–793)] ^b | | | |
| | maintenance | 13/n.s. [265 (141–453)] ^b | | | |
| | polymerisation | 15/n.s. [251 (140–414)] ^b | | | |
| | coagulation | 7/n.s. [248 (100–511)] ^b | | | |
| | cumulative butadiene exposure (ml/m ³ × years) ^c | observed cases/SMR | | | |
| | 0 | 8/76 | | | |
| | <1 | 4/41 | | | |
| | 1–19 | 12/133 | | | |
| | 20–79 | 16/166 | | | |
| | >79 | 18/264 | | | |

Table 1. continued

| Literature reference cohort | Exposure | Leukaemia ^a [SMR (95% CI)] | Lymphosarcoma ^a [SMR (95% CI)] | Other LHC ^a [SMR (95% CI)] | All LHC ^a [SMR (95% CI)] |
|--|-----------------------|--|--|--|---|
| Divine and Hartman (1996) 2795 employees in 1,3-butadiene production | 1942–1994 | 13/11.5 [113 (60–193)] | 9/4.7 [191 (87–364)] | 20/12.4 [161 (98–250)] | 42/28.6 [147 (106–198)] ^b |
| | worked for < 5 years | 8/5.4 [147 (64–292)] | 6/2.3 [261 (n.s.)] | 8/5.9 [136 (58–268)] | 22/13.6 [162 (101–245)] ^b |
| | beginning before 1946 | 7/7.0 [100 (40–206)] | 7/2.9 [241 (97–497)] | 11/6.9 [159 (79–286)] | 25/16.8 [148 (96–219)] |
| | exposure level: | | | | |
| | background | 0/0.6 [0 (0–591)] | | | |
| | low | 2/1.8 [109 (12–395)] | | | |
| | varied | 7/2.8 [249 (100–513)] ^b | | | |
| Ward <i>et al.</i> (1995) 364 employees in 1,3-butadiene production | 1941–1971 | 2/1.6 [123 (15–444)] | 4/0.7 [577 (157–1480)] ^b | 1/1.64 [61 (1–339)] | 7/4.0 [175 (70–361)] |

^a number of deaths observed/expected^b significantly increased SMR^c from Macaluso *et al.* (1996), trend test significant ($p < 0.01$)

n.s. not specified

4 Effects on Animals

4.1 Reproductive and developmental toxicity

An inhalation teratogenicity study (Hazleton Laboratories 1982) was carried out with rats exposed for 6 hours daily from day 6 to day 15 of gestation to 1,3-butadiene concentrations of 200, 1000 or 8000 ml/m³. In the dams exposed to 8000 ml/m³, delayed growth was observed. In this group the foetal weights were also smaller than the control values. Foetal defects (lens cloudiness, visceral, cardiovascular and facial abnormalities, cryptorchidism and ossification disorders of the sternum and ribs, malformations of the skull, spine, sternum and the long bones) were recorded in the group exposed to 8000 ml/m³ but not in the animals exposed to lower concentrations.

4.2 Genotoxicity

4.2.1 *In vitro* studies

It has been demonstrated in animal studies that 1,3-butadiene is subject to intermediary metabolism to its epoxide 1,2-epoxy-3-butene (see Section 2 Metabolism and Metabolic Activation). Both this epoxide and 1,3-butadiene were shown to be mutagenic in the *Salmonella typhimurium* strains TA1530 and TA1535 (De Meester *et al.* 1978). The mutagenic effects of the butadiene monoepoxide, 1,2-epoxy-3-butene, were confirmed in a test in *Escherichia coli* WP2; the substance was also shown to have alkylating activity in a test with 4-(*p*-nitrobenzyl)pyridine as nucleophile (Hemminki *et al.* 1980).

4.2.2 *In vivo* studies

A detailed review of recent data for the *in vivo* genotoxicity of 1,3-butadiene has been published by Pacchierotti *et al.* (1998). Decisive for the classification of 1,3-butadiene in Germ cell mutagen group 2 were the recent studies of germ cell mutagenicity which demonstrated that exposure of male mice to inhaled 1,3-butadiene induced dominant lethal mutations in sperm and spermatids (Adler and Anderson 1994, Adler *et al.* 1994, Anderson *et al.* 1993). The lowest effective exposure concentration was 65 ml/m³ (6 hours/day, 5 days/week, 4 weeks) (Anderson *et al.* 1998). In addition, heritable translocations were induced in the sperm and spermatids of the mouse (Adler *et al.* 1995). The dose-response relationship was linear in the range between 0, 500 and 1300 ml/m³ (6 hours/day for 5 days) (Adler *et al.* 1998). The potential genetic risk calculated on the basis of these data revealed that, for workers exposed to an average 1,3-butadiene concentration of 1.58 ml/m³, an incidence of 256–380 × 10⁻⁶ children bearing translocations is to be expected (Pacchierotti *et al.* 1998). The spontaneous incidence of translocations

in the human population is 879×10^{-6} (Sankaranarayanan 1982). After exposure of male rats to exposure concentrations as high as 1250 ml/m^3 (6 hours/day, 5 days/week for 10 weeks) no dominant lethal mutations were observed (Anderson *et al.* 1998). Presumably the lower level oxidative metabolism of the rat plays a role here.

4.3 Carcinogenicity

A long-term study was carried out with Sprague-Dawley CD rats (Hazleton Laboratories 1981). Groups of 110 female and 110 male rats were exposed 6 hours/day, 5 days/week for 105 (♀) or 111 (♂) weeks to 1,3-butadiene concentrations of 0 ml/m^3 (controls), 1000 or 8000 ml/m^3 . The exposure concentrations were chosen after a 3-month range-finding study (Crouch *et al.* 1979a, 1979b). Adequate exposure controls were included and the purity of the 1,3-butadiene used was checked. The results obtained are listed below.

- In the groups exposed to 8000 ml/m^3 , increased discharge from the eyes and nose was seen in months 2 to 5; at the same time “mild ataxia” was recorded, suggestive of CNS depression.
- Exposed female animals developed palpable nodules in the mammary glands more frequently than did the control animals.
- Mortality tended to increase in the exposed groups (♀, ♂) in a dose-dependent manner.

Evaluation of the **tumour incidences** demonstrated that the incidence of Leydig cell tumours and exocrine pancreas tumours (in ♂) and that of malignant mammary tumours, tumours of the stroma of uterus and vagina and thyroid tumours (in ♀) were increased in the exposed groups. Details are shown in Table 2.

Table 2. Tumour incidences in 110 ♀ and 110 ♂ rats exposed by inhalation to 1,3-butadiene (Hazleton Laboratories 1981)

| Tumour location | Controls | 1,3-Butadiene | |
|--|----------|----------------------|----------------------|
| | | 1000 ml/m^3 | 8000 ml/m^3 |
| malignant mammary tumours (animals which died) | 3 ♀ | 6 ♀ | 14 ♀ |
| incidental mammary tumours | 17 ♀ | 14 ♀ | 22 ♀ |
| Leydig cell tumours | 0 | 3 ♂ | 8 ♂ |
| thyroid gland tumours | 0 | 4 ♀ | 11 ♀ |
| pancreas tumours | 2 ♂ | 1 ♂ | 9 ♂ |
| Zymbal gland tumours | 0 | 1 ♂ | 1 ♂, 3 ♀ |
| tumours of uterus and vagina | 1 ♀ | 4 ♀ | 5 ♀ |

From the tumour incidences and the clear dose-dependence it was concluded that the results demonstrate a weak carcinogenic effect of 1,3-butadiene (Hazleton Laboratories 1981).

In a long-term study with another species, the B6C3F₁ mouse, the carcinogenic effects of 1,3-butadiene were confirmed. Malignant tumours were induced in mice exposed to

concentrations below 1000 ml/m³. The studies were carried out as a part of the American “National Toxicology Program” (NTP 1984). Groups of 50 male and 50 female B6C3F₁ mice were exposed for 6 hours/day, 5 days/week to 1,3-butadiene concentrations of 0 (controls), 625 or 1250 ml/m³. After 60 (♂) and 61 (♀) weeks the study was discontinued because so many of the treated animals had died with malignant tumours. At this time the tumour incidences listed in Table 3 were recorded. In addition, the incidence of morphologically visible liver damage and of damage to the epithelium of the respiratory tract was increased in the exposed animals.

Table 3. Incidence of tumours in groups of 50 male and 50 female mice exposed to 1,3-butadiene (NTP 1984)

| Tumours | Male mice (60 weeks) | | | Female mice (61 weeks) | | |
|--|----------------------|--------------------------|---------------------------|------------------------|--------------------------|---------------------------|
| | controls | 625 ml/m ³ | 1250 ml/m ³ | controls | 625 ml/m ³ | 1250 ml/m ³ |
| cardiac haemangiosarcomas | 0/50 | 16/49 | 7/49 | 0/50 | 11/48 | 18/49 |
| malignant lymphomas | 0/50 | 23/50 | 29/50 | 1/50 | 10/49 | 10/49 |
| adenomas and carcinomas of the bronchi and lungs | 2/50 | 14/49 | 15/49 | 3/49 | 12/48 | 23/49 |
| forestomach | | | | | | |
| – epithelial hyperplasia | 0/49 | 5/40 | 7/44 | 0/49 | 5/42 | 9/49 |
| – papillomas | 0/49 | 5/40 | 0/44 | 0/49 | 4/42 | 10/49 |
| – squamous cell carcinomas | 0/49 | 2/40 | 1/44 | 0/49 | 1/42 | 1/49 |
| mammary gland | | | | | | |
| – acinar cell adenomas | | | | 0/50 | 2/49 | 6/49 |
| – adenosquamous carcinomas | | | | 0/50 | 4/49 | 0/49 |
| ovaries | | | | | | |
| – granulosa cell tumours | | | | 0/49 | 6/45 | 12/48 |
| – granulosa cell carcinomas | | | | 0/49 | 0/49 | 1/48 |

The early development of tumours (cardiac haemangiosarcomas, malignant lymphomas, adenomas and carcinomas of the lungs and bronchi, stomach papillomas, mammary tumours and ovary tumours) and their increased incidence was interpreted as clear evidence of carcinogenicity of 1,3-butadiene.

Both the monoepoxide and the diepoxide of 1,3-butadiene were shown to induce tumours after subcutaneous and epicutaneous administration (van Duuren *et al.* 1963, van Duuren 1965, van Duuren *et al.* 1965, 1966)

5 Manifesto (MAK value/classification)

The available results of epidemiological studies suggest that exposure during production of 1,3-butadiene leads to an increased risk of developing lymphosarcoma. For employees in the production of synthetic rubber, where exposure is to a mixture of styrene,

1,3-butadiene, rubber and other substances, the risk of developing leukaemia is increased. The localization (leukaemia) does not suggest a clear association with 1,3-butadiene exposure, because this could not be demonstrated for workers in 1,3-butadiene production. The difference in localization cannot be accounted for entirely in terms of diagnostic uncertainties. The epidemiological data are sufficient to classify 1,3-butadiene as a human carcinogen, especially as the substance is carcinogenic in animal studies. Therefore 1,3-butadiene is classified in Category 1 of Section III of the *List of MAK and BAT Values*.

Germ cell mutagenicity studies show that inhalation exposure of male mice to 1,3-butadiene induces dominant lethal mutations and heritable translocations in sperm and spermatids. Therefore 1,3-butadiene is classified in Germ cell mutagen category 2. A MAK value cannot be established.

6 References

- Adler I-D, Anderson D (1994) Dominant lethal effects after inhalation exposure to 1,3-butadiene. *Mutat Res* 309: 295–297
- Adler I-D, Cao J, Filser JG, Gassner P, Kessler W, Kliesch U, Neuhäuser-Klaus A, Nüsse M (1994) Mutagenicity of 1,3-butadiene inhalation in somatic and germinal cells of mice. *Mutat Res* 309: 307–314
- Adler I-D, Filser JG, Gassner P, Kessler W, Schöneich J, Schriever-Schwemmer G (1995) Heritable translocations induced by inhalation exposure of male mice to 1,3-butadiene. *Mutat Res* 347: 121–127
- Adler I-D, Filser J, Gonda H, Schriever-Schwemmer G (1998) Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germ cells of male mice. *Mutat Res* 397: 85–92
- Albrecht OE, Filser JG, Neumann H-G (1993) Biological monitoring of 1,3-butadiene: species differences in haemoglobin binding in rat and mouse. in: Sorsa M, Peltonen K, Vainio H, Hemminki K (Eds) *Butadiene and styrene: assessment of health hazards, IARC Scientific Publications No 127*, IARC, Lyon, 135–142
- Anderson D, Edwards AJ, Brinkworth MH (1993) Male-mediated F₁ effects in mice exposed to 1,3-butadiene. in: Sorsa M, Peltonen K, Vainio H, Hemminki K (Eds) *Butadiene and styrene: assessment of health hazards, IARC Scientific Publications No 127*, IARC, Lyon, 171–181
- Anderson D, Hughes JA, Edwards AJ, Brinkworth MH (1998) A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. *Mutat Res* 397: 77–84
- Au WW, Bechtold WE, Whorton Jr EB, Legator MS (1995) Chromosome aberrations and response to γ -ray challenge in lymphocytes of workers exposed to 1,3-butadiene. *Mutat Res* 334: 125–130
- Bolt HM, Schmiedel G, Filser JG, Rolzhauser HP, Lieser K, Wistuba D, Schurig V (1983) Biological activation of 1,3-butadiene to vinyl oxirane by rat microsomes and expiration of the reactive metabolite by exposed rats. *J Cancer Res Clin Oncol* 106: 112–116
- Bond GG, Bodner KM, Olsen GW, Cook RR (1992) Mortality among workers engaged in the development or manufacture of styrene-based products – an update. *Scand J Work Environ Health* 18: 145–154
- Carpenter CP, Shaffer CB, Weil CS, Smyth HF (1944) Studies on the inhalation of 1,3-butadiene; with a comparison of its narcotic effect with benzol, toluol, and styrene, and a note on the elimination of styrene by the human. *J Indust Hyg* 26: 69–78

- Cowles SR, Tsai SP, Snyder PJ, Ross CE (1994) Mortality, morbidity, and haematological results from a cohort of long-term workers involved in 1,3-butadiene monomer production. *Occup Environ Med* 51: 323–329
- Crouch CN, Pullinger DH, Dare PR (1979a) Inhalation toxicity studies with 1,3-butadiene – 1. atmosphere generation and control. *Am Ind Hyg Assoc J* 40: 796–802
- Crouch CN, Pullinger DH, Gaunt IF (1979b) Inhalation toxicity studies with 1,3-butadiene – 2. 3 month toxicity study in rats. *Am Ind Hyg Assoc J* 40: 796–802
- Delzell E, Sathiakumar N, Macaluso M, Hovinga M, Larson R, Barbone F, Beall C, Cole P (1996) A follow-up study of synthetic rubber workers. *Toxicology* 113: 182–189
- Divine BJ, Hartmann CM (1996) Mortality update of butadiene production workers. *Toxicology* 113: 196–181
- Downs T, Pier S, Crane M, Yim K, Kim K (1993) Cause-specific mortality in a cohort of 1000 ABS workers. Presented at international symposium on health hazards of butadiene and styrene, Espoo, Finland, 18.–21.04.1993, cited in: ECETOC (1997)
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1997) Special report No. 12: *1,3-butadiene, OEL criteria document* (second edition), ECETOC, Brussels
- Elovaara E, Osterman-Golkar S, Nakajima T, Gelboin HV, Riihimäki V, Sorsa M (1994) 1,3-Butadiene exposure of rats: hemoglobin adducts of 1,2-epoxybutene and cytochrome P450-related changes in styrene metabolism. in: Lechner MC (Ed.) *Cytochrome P450*, Libbey Eurotext, Paris, 567–570
- Hayes RB, Xi L, Bechtold WE, Rothman N, Yao M, Henderson R, Zhang L, Smith MT, Zhang D, Wiemels J, Dosemeci M, Yin S, O'Neill JP (1996) Hprt mutation frequency among workers exposed to 1,3-butadiene in China. *Toxicology* 113: 100–105
- Hazleton Laboratories Europe (1981) *The toxicity and carcinogenicity of butadiene gas administered to rats by inhalation for approximately 24 months*, Final report No. 2653-522/2, Hazleton Laboratories, Harrowgate HG3 1PY, England
- Hazleton Laboratories Europe (1982) *1,3-Butadiene: Inhalation teratogenicity study in the rat* Final report and addendum No. 2788-522/3, Hazleton Laboratories, Harrowgate HG3 1PY, England
- Hemminki K, Falck K, Vainio H (1980) Comparison of alkylation rates and mutagenicity of directly acting industrial and laboratory chemicals: epoxides, glycidyl ethers, methylating and ethylating agents, halogenated hydrocarbons, hydrazine derivatives, aldehydes, thiuram and dithiocarbamate derivatives. *Arch Toxicol* 46: 277–285
- Himmelstein MW, Acquavella JF, Recio K, Medinsky M, Bond JA (1997) Toxicology and epidemiology of 1,3-butadiene. *Crit Rev Toxicol* 27: 1–108
- Landrigan PJ (1993) Critical assessment of epidemiological studies on the carcinogenicity of 1,3-butadiene and styrene. in: Sorsa M, Peltonen K, Vainio H, Hemminki K (Eds) *Butadiene and styrene: assessment of health hazards, IARC Scientific Publications No. 127*, IARC, Lyon, 375–388
- Legator MS, Au WW, Ammenheuser M, Ward Jr JB (1993) Elevated somatic cell mutant frequencies and altered DNA repair responses in nonsmoking workers exposed to 1,3-butadiene. in: Sorsa M, Peltonen K, Vainio H, Hemminki K (Eds) *Butadiene and styrene: assessment of health hazards, IARC Scientific Publications No 127*, IARC, Lyon, 253–263
- Macaluso M, Larson R, Delzell E, Sathiakumar N, Hovinga, Julian J, Muir D, Cole P (1996) Leukemia and cumulative exposure to butadiene, styrene and benzene among workers in the synthetic rubber industry. *Toxicology* 113: 190–202
- Malvoisin E, Lhoest G, Poncelet F, Roberfroid M, Mercier M (1979) Identification and quantitation of 1,2-epoxybutene-3 as the primary metabolite of 1,3-butadiene. *J Chromatog* 178: 419–426
- Malvoisin E, Roberfroid M (1982) Hepatic microsomal metabolism of 1,3-butadiene. *Xenobiotica* 12: 137–144

- Malvoisin E, Mercier M, Roberfroid M (1982) Enzymatic hydration of butadiene monoxide and its importance in the metabolism of butadiene. in: Snyder R, Parke DV, Kocsis JJ, Jollow DJ, Gibson GG, Witmer CM (Eds) *Biological Reactive Intermediates*, Vol. II, Part A, Plenum Publishing Corp New York/London, p 437-444
- Matanoski GM, Santos-Burgoa C, Schwartz L (1990) Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943–1982). *Environ Health Perspect* 86: 107–117
- de Meester C, Poncelet F, Roberfroid M, Mercier M (1978) Mutagenicity of butadiene and butadiene monoxide. *Biochem Biophys Res Commun* 80: 298–305
- Meinhardt TJ, Lemen RA, Crandall MS, Young RJ (1982) Environmental epidemiologic investigation of styrene-butadiene rubber industry. *Scand J Work Environ Health* 8: 250–259
- NIOSH (National Institute for Occupational Safety and Health) (1979) *Registry of Toxic Effects of Chemical Substances*, Vol. I. National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA
- NTP (National Toxicology Program) (1984) *NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F₁ mice (Inhalation Studies) NTP-83-071*. NIH Publication No. 84-2544, US Dept of Health and Human Services, Washington, DC, USA
- Osterman-Golkar SM, Kautiainen A, Bergmark E, Håkansson K, Mäki-Paakkanen J (1991) Hemoglobin adducts and urinary mercapturic acids in rats as biological indicators of butadiene exposure. *Chem Biol Interact* 80: 291–302
- Osterman-Golkar SM, Bond JA, Ward JB, Legator MS (1993) Use of hemoglobin adducts for biomonitoring exposure to 1,3-butadiene. in: Sorsa M, Peltonen K, Vainio H, Hemminki K (Eds) *Butadiene and styrene: assessment of health hazards*, IARC Scientific Publications No. 127, IARC, Lyon, 127–134
- Osterman-Golkar S, Peltonen K, Anttinen-Klemetti T, Landin HH, Zorcec V, Sorsa M (1996) Haemoglobin adducts as biomarkers of occupational exposure to 1,3-butadiene. *Mutagenesis* 11: 145–149
- Pacchierotti F, Adler I-D, Anderson D, Brinkworth M, Demopoulos NA, Lähde tie J, Osterman-Golkar S, Peltonen K, Russo A, Tates A, Waters R (1998) Genetic effects of 1,3-butadiene and associated risk for heritable damage. *Mutat Res* 397: 93–115
- Pérez HL, Lähde tie J, Landin H, Kilpeläinen I, Koivisto P, Peltonen K, Osterman-Golkar S (1997) Haemoglobin adducts of epoxybutanediol from exposure to 1,3-butadiene or butadiene epoxides. *Chem Biol Interact* 105: 181–198
- Peschel C (1997) Letter to the DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
- Sankaranarayanan K (1982) *Genetic effects of ionizing radiation in multicellular eukaryotes and the assessment of genetic radiation hazard in man*, Elsevier, Amsterdam, 190
- van Sittert NJ, van Vliet EWN (1994) Monitoring occupational exposure to some industrial chemicals by determining hemoglobin adducts. *Clin Chem* 40: 1472–1475
- Sorsa M, Autio K, Demopoulos NA, Järventaus H, Rössner P, Šrám RJ, Stephanou G, Vlachodimitropoulos D (1994) Human cytogenetic biomonitoring of occupational exposure to 1,3-butadiene. *Mutat Res* 309: 321–326
- Sorsa M, Osterman-Golkar S, Peltonen K, Saarikoski ST, Šrám R (1996) Assessment of exposure to butadiene in the process industry. *Toxicology* 113: 77–83
- Steenland K, Dedens J, Salvan A, Stayner L (1996) Negative bias in exposure-response trends in occupational studies: modeling the healthy worker survivor effect. *Am J Epidemiol* 143: 202–210
- Tates AD, van Dam FJ, de Zwart FA, Darroudi F, Natarajan AT, Rössner P, Peterková K, Peltonen K, Demopoulos NA, Stephanou G, Vlachodimitropoulos D, Šrám RJ (1996) Biological effect monitoring in industrial workers from the Czech Republic exposed to low levels of butadiene. *Toxicology* 113: 91–99
- Van Duuren BL (1969) Carcinogenic epoxides, lactones and halo-ethers and their mode of action. *Ann NY Acad Sci* 163: 633–651

- Van Duuren BL, Nelson N, Orris L, Palmes ED, Schmitt F (1963) Carcinogenicity of epoxides, lactones, and peroxy compounds. *J Natl Cancer Inst* 31: 41-55
- Van Duuren BL, Orris L, Nelson N (1965) Carcinogenicity of epoxides, lactones and peroxy compounds II. *J Natl Cancer Inst* 35: 707-717
- Van Duuren BL, Langseth L, Orris L, Teebor G, Nelson N, Kuschner M (1966) Carcinogenicity of epoxides, lactones and peroxy compounds IV. Tumor response in epithelial and connective tissue in mice and rats. *J Natl Cancer Inst* 37: 825-838
- Ward Jr JB, Ammenheuser MM, Bechtold WE, Whorton Jr EB, Legator MS (1994) hprt mutant lymphocyte frequencies in workers at a 1,3-butadiene production plant. *Environ Health Perspect* 102, Suppl 9: 79-85
- Ward EM, Fajen JM, Ruder AM, Rinsky RA, Halperin WE, Fessler-Flesch CA (1995) Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. *Environ Health Perspect* 103: 598-603
- Ward Jr B, Ammenheuser MM, Whorton Jr BW, Bechtold WE, Kelsey KT, Legator MS (1996) Biological monitoring for mutagenic effects of occupational exposure to butadiene. *Toxicology* 113: 84-90

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Safety Assessment of Styrene and Vinyl-type Styrene Copolymers as Used in Cosmetics

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The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

ABSTRACT: These styrene and vinyl-type styrene copolymers function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products. After considering the large sizes of these molecules, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of toxicity tests provided the Panel with a sufficient basis to assess the safety of these polymers as used in cosmetics. The Panel concluded that the 35 styrene and vinyl-type styrene copolymers are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment.

INTRODUCTION

This report presents information relevant to evaluating the safety of styrene and vinyl-type styrene copolymers as used in cosmetics. Film-former is the most frequent function reported for these ingredients. Other common functions include opacifying agent and viscosity increasing agent. Given the toxicity of two of the component monomers present in styrene and vinyl-type styrene copolymers, styrene and 1,3-butadiene, carcinogenicity data on these monomers are included. Styrene is a component of all of the copolymers reviewed in this safety assessment; however, butadiene monomer is a component of only three copolymers included in this review.

CHEMISTRY

Definition and Structure

Polystyrene is the polymerization product of vinylbenzene (a.k.a. styrene). The other ingredients in this report are all vinyl-type copolymers with vinylbenzene. The term “vinyl-type copolymers” means that all of the monomers, utilized to make these polymer ingredients, have in common an ethylene unit whose pi electrons are directly involved in the polymerization process. Typically, a catalyst is utilized to initiate the polymerization.¹ There is a large multitude of relevant initiating catalysts, ranging from UV light to Ziegler-Natta-type catalysts, which can result in a variety of differences in the characteristics (e.g. crystallinity and resultant hardness) of the copolymer formed. The synthesis of these ingredients is typically carried out in one or more organic solvents, with one or more catalysts.

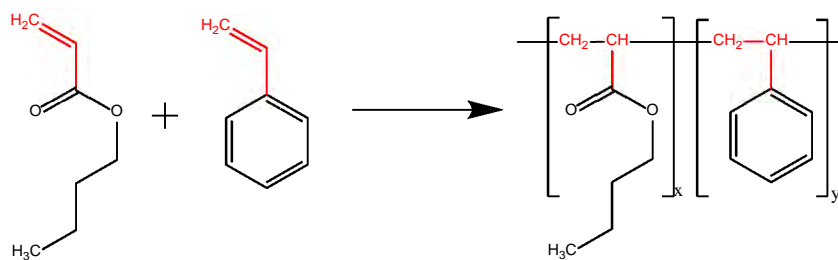


Figure 1. Butylacrylate/Styrene Copolymer

These ingredients are high molecular weight, large molecular volume, and inert polymers. While not truly soluble, these ingredients may be swellable in certain organic solvents.

The molecular structures and definitions of styrene and vinyl-type styrene copolymers are presented in Table 1.²

Physical and Chemical Properties

Polystyrene

Properties of polystyrene are presented in Table 2.^{3,4,5} Some of the properties include physical state (colorless solid in various forms), molecular mass (10,000 to 300,000), relative density (1.04 to 1.13), melting point (240°C), flash point (345 to 360°C), and auto-ignition temperature (427°C).

The thermal degradation of high impact polystyrene to styrene and other thermal degradation products occurred at a temperature of 250°C.⁶ Reportedly, the principal limitations of polystyrene in industry are brittleness, inability to withstand the temperature of boiling water, and poor oil resistance.⁷ Thus, polystyrene is often modified, e.g., by copolymerization with acrylonitrile and/or butadiene. Regarding this process, the most common styrene polymers are poly(acrylonitrile-butadiene-styrene) and styrene-butadiene copolymer.

Styrene

Styrene is a component of each styrene and vinyl-type styrene copolymer reviewed in this safety assessment. The vinyl group of styrene is reactive, and styrene polymerizes at a significant rate at room temperature.⁸ Polymerization proceeds more rapidly at elevated temperatures or in the presence of many commonly available reagents. Commercially available grades of styrene contain an inhibitor of styrene polymerization (e.g., 4-*t*-butylcatechol). Additionally, upon exposure to light and air, styrene undergoes polymerization and oxidation, with the formation of peroxides.⁴ Additional properties of styrene are presented in Table 3.⁴

Styrene-Butadiene Copolymer

Properties of styrene-butadiene copolymer are presented in Table 4.⁵

1,3-Butadiene

Properties of 1,3-butadiene are presented in Table 5.⁹

Composition/Impurities

Polystyrene

Polystyrene is available in the United States in a variety of grades, and the following are considered major grades:⁵ (1) crystalline or straight polystyrene, (2) impact-modified grades, which typically contain approximately 5% polybutadiene elastomer, and (3) expandable beads, which contain a small amount of *n*-pentane entrapped in each globule.

During the early years of polystyrene production, the residual monomer content was as high as 2%, and, at the beginning of the 1960's, it was approximately 1%.¹⁰ Composition/impurities data from a 2013 safety dossier on a polystyrene trade name material summarized in Table 6 indicates that the residual monomer content of polystyrene is < 5 ppm. Furthermore, data summarized in Table 6 indicate that other styrene and vinyl-type styrene copolymer trade name materials contain styrene monomer at levels of < 100 ppm or less.

Styrene-Butadiene Copolymer

The following styrene-butadiene copolymers are available in the United States:⁵ (1) styrene-butadiene elastomers (commonly called SBR, or styrene-butadiene rubber), (2) styrene block polymers with butadiene, and (3) styrene-butadiene copolymer latexes. Dry SBR (produced by emulsion polymerization) contains styrene units (23% to 25%) and butadiene units (75% to 77%) on a polymer basis. When produced via solution polymerization, the composition of dry SBR varies; however, typical grades contain styrene units (~ 10% to 25%) and butadiene units (75% to 90%). Styrene block polymers with butadiene are available with a styrene content of 25% to 50%, and the most widely used grades contain 30% styrene units.

Trade Name Materials

Composition/impurities data on styrene and vinyl-type styrene copolymer trade name materials included in this safety assessment are presented in Table 6. Data on properties of these trade name materials are also included.

Methods of Production

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer

The ethylene/propylene/styrene copolymer and butylene/ethylene/styrene copolymer used as thickeners are made by anionic polymerization, which results in little or no residual monomer in the polymer.¹¹

Polystyrene

Polystyrene is produced from styrene by mass, solution, suspension, or emulsion polymerization processes.⁷ Polystyrene resins are typically produced by a modified mass polymerization process in a continuous manner.⁵ The liquid styrene monomer is diluted with a relatively small amount of a diluent, e.g., 5% to 15% of ethylbenzene. In some cases, more diluent is used, and the process may then be called a solution process. The heated mixture of styrene, solvent, and initiator is reacted at 120°C to 160°C. Unreacted monomer and solvent are removed after polymerization is complete.

Styrene/Butadiene Copolymer

Dry SBR is produced via an emulsion polymerization (cold or hot) or solution polymerization process.⁵ Composition data on styrene/butadiene copolymer resulting from either process are presented in the Composition/Impurities section.

The following components (in parts per 100 monomer) comprise a typical recipe for SBR produced by cold emulsion polymerization:⁵ butadiene (70), styrene (30), water (180), fatty acid soap (2.25), disproportioned rosin soap (2.25), potassium chloride (0.3), potassium hydroxide (0.3), *t*-dodecyl mercaptan (0.23), sodium formaldehyde β -naphthalene sulfonate (0.04), sodium formaldehyde sulfoxylate (0.04), *p*-methane hydroperoxide (0.04), tetrasodium ethylenediaminetetraacetate (0.025), and ferrous sulfate heptahydrate.

A typical recipe (component data in parts per 100 monomer) for SBR produced by hot emulsion polymerization is as follows:⁵ butadiene (75), styrene (25), water (180), fatty acid or rosin soap (5), *n*-dodecyl mercaptan (0.5), and potassium persulfate (0.3).

Recipes for SBR produced by solution polymerization are said to vary greatly, and depend upon the properties desired.⁵ SBR is vulcanized (typically 1.5 to 2.0 parts sulfur per 100 parts of polymer are used). Furthermore, accelerators, antioxidants, activators, fillers (e.g., carbon black), and softeners may be used, depending on the properties of the finished rubber that are desired. SBR is also extended with aromatic and naphthenic oils to improve handling and processing.

Styrene block copolymers with butadiene are typically produced by anionic solution polymerization with *sec*-butyllithium or *n*-butyllithium in a solvent such as cyclohexane, isopentane, *n*-hexane, or mixtures.⁵ The styrene is homopolymerized, followed by the addition of butadiene; more styrene is then added. The polymer is coagulated from the solution with water. Styrene block polymers are usually compounded with fillers, extenders oils, and, sometimes, other polymers (e.g., polyindene or polystyrene).

USE

Cosmetic

Styrene and vinyl-type styrene copolymers function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products.²

Information on the use of these ingredients as a function of product type was supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP).¹² The highest use frequency was reported for ethylene/propylene/styrene copolymer, followed by butylene/ethylene/styrene copolymer. The Personal Care Products Council conducted a survey of ingredient use concentrations in 2013-2014, and maximum use concentrations ranging from 0.000038% (styrene/VP copolymer, in skin care preparations) to 36.5% (polystyrene, in skin cleansing products) were reported.¹³ The highest maximum reported use concentrations for rinse-off and leave on products were 36.5% (polystyrene) and 35% (styrene/acrylates copolymer, in basecoats and undercoats), respectively. Ingredient frequency of use and concentration data are presented in Table 7.

Cosmetic products containing styrene and vinyl-type styrene copolymers may be applied to the skin and hair or, incidentally, these products may come in contact with the eyes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

The following ingredients are used in products that are sprayed (maximum concentrations reported): hair sprays (styrene/acrylates copolymer [0.35%,]; styrene/VP copolymer [0.12%, in pump spray]), suntan sprays (styrene/acrylates copolymer [3.5%]), and body and hand sprays (ethylene/propylene/styrene copolymer [0.5%]). Additionally, isobutylene/styrene copolymer is used in face powders at a maximum concentration of 1%. Because styrene/acrylates copolymer, styrene/VP copolymer, and ethylene/propylene/styrene copolymer are used in products that are sprayed and isobutylene/styrene copolymer is used in face powders they could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.^{14,15,14,16} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{14,15}

Noncosmetic

Polystyrene

Polystyrene is used as a plasticizer in the bottled water industry, and studies have shown that styrene leaches continuously from polystyrene bottles.¹⁷ The skin adhesive layer of a pressure ulcer preventive dressing may contain styrene block copolymer as an adhesive compound.¹⁸ Polystyrene foam is widely used for thermal insulation.⁷

Additionally, polystyrene may be safely used as a component of articles intended for use in contact with food. For this purpose, polystyrene shall contain not more than 1 weight percent of total residual styrene monomer.¹⁹ The exception to this limit relates to use in contact with fatty foods, whereas such polystyrene basic polymers shall contain not more than 0.5 weight percent of total residual styrene monomer.

Styrene

Styrene is listed among the synthetic flavoring substances and adjuvants that may be safely used in food.²⁰ It should be used in the minimum quantity required to produce the intended effect, and, otherwise, in accordance with all principles of good manufacturing practice.

Styrene/Butadiene Copolymer

Butadiene-styrene rubber (styrene/butadiene copolymer) is included on the list of FDA-approved direct food additives.²¹

TOXICOKINETICS

Styrene

Nine male volunteers were exposed for 10 to 30 minutes by dipping one hand in liquid styrene. Urine and breath were sampled periodically for metabolites (mandelic and phenylglyoxylic acids) and styrene analyses respectively. The results obtained show that the rate of absorption of styrene through the skin was very low, averaging $1 \pm 0.5 \mu\text{g}/\text{cm}^2/\text{minute}$.^{22,23}

A field study comparing the urinary excretion of styrene metabolites in 4 groups of workers who performed the same task, but wore different protective equipment, was performed.²² It was concluded that the percutaneous absorption of styrene was not an important contribution to the body burden.

Several studies have suggested that styrene accumulates in the subcutaneous fat.²² However, based on the measurement of urinary metabolites, there was no styrene accumulation in workers exposed to 37 ppm (160 mg/m³) styrene in air during the work week.

Styrene is primarily metabolized to styrene 7,8-oxide by cytochrome P450 (CYP) enzymes.²² Epoxide hydrolase metabolizes the oxide to phenylethylene glycol, and then to mandelic, phenylglyoxylic, and benzoic acids. Additional routes of metabolism include ring hydroxylation, but this appears to be a minor pathway in humans. Another pathway is the conversion of styrene to 1- and 2-phenylethanol, which is further metabolized to phenylacetaldehyde, phenylacetic acid, phenylacetic acid, and hippuric acid. Styrene 7,8-oxide may also be metabolized by conjugation with glutathione to form mercapturic acids. The conversion of styrene to mercapturic acids, considered a minor pathway in humans, is < 1% of the absorbed dose of styrene.²⁴

Small amounts of styrene (0.7% to 4.4%) are exhaled unchanged.²² This finding has been confirmed in additional studies in which 0.7% to 2.2% of the amount of inhaled styrene was found unchanged in the exhaled breath of 4 subjects exposed to 50 ppm (213 mg/m³) styrene in air for 2 h. Small amounts of styrene are also excreted unmetabolized in the urine.

The pharmacokinetics of inhaled styrene (80 ppm [341 mg/m³]) was studied using 4 volunteers.^{22,25} Calculated half-life values of 0.6 h and 13.0 h for the 2 phases of elimination were reported. In a study of blood styrene concentrations in 76 exposed workers at the end of their work shift and in the morning thereafter, the half-life of blood styrene was 3.9 h at 16 h after the end of the workshift.

1,3-Butadiene and Styrene

Nine minutes after rabbits were exposed to 1,3-butadiene at concentrations of 250,000 ppm in air, the test chemical was found in the femoral artery at a concentration of 0.26 mg/ml and in the femoral vein at a concentration of 0.18 mg/ml.²⁶

Mice and rats were exposed (dynamic flow exposure: 2 h [mice] and 4 h [rats]) to butadiene or styrene vapors at the following concentrations: 270 mg/liter (butadiene [mice]), 285 mg/liter (butadiene [rats]), 21 mg/liter (styrene [mice]), and 11.8 mg/liter (styrene [rats]).^{26,27} The number, strain, and sex of the animals tested were not specified. Following exposure, the concentrations of butadiene and styrene in tissues were determined by gas liquid chromatography. Various tissues from rats were analyzed, but only brain tissue from mice was analyzed. Mean concentrations in tissues from rats are included below:

- 50.8 mg butadiene/100g brain (10 tests)
- 25 mg styrene/100g brain (7 tests)

- 51.4 mg butadiene/100g liver (10 tests)
- 20 mg styrene/100g liver (7 tests)
- 36.3 mg butadiene/100g kidney (7 tests)
- 14.7 mg styrene/100g kidney (7 tests)
- 45 mg butadiene/100g spleen (7 tests)
- 19.1 mg styrene/100 g spleen (7 tests)
- 152.1 mg butadiene/100g perinephric fat (7 tests)
- 132.8 mg styrene/100g perinephric fat (7 tests)

Mean concentrations in brain tissue from mice were 54.4 mg butadiene/100cc brain (10 tests) and 18.02 mg styrene/100cc brain (7 tests). In a subsequent experiment series (rats, same procedure), mean concentrations in the brain and liver were determined at various times for up to 90 minutes after removal from the chamber. By 90 minutes, mean tissue concentrations were:^{26,27}

- 0 to traces of butadiene/100cc brain (4 tests)
- traces to 4.4 mg styrene/100 cc brain (4 tests)
- 0 to traces of butadiene/100cc liver (4 tests)
- 5.2 to 11 mg styrene/100cc liver (4 tests)

The first step in butadiene metabolism involves cytochrome P450 (CYP)-mediated oxidation to epoxybutene.⁹ At low concentrations of butadiene, metabolism via CYP2E1 predominates. Epoxybutene may be metabolized by conjugation with glutathione (GSH), mediated by glutathione *S*-transferase (GST), or by hydrolysis, catalyzed by epoxide hydrolase (EH). Epoxybutene may also be oxidized to multiple diastereomers of diepoxybutane. Dihydroxybutene formed by hydrolysis of epoxybutene may be oxidized to epoxybutanediol. The latter epoxides are also detoxified by GST or EH. The partial hydrolysis of diepoxybutane also produces epoxybutanediol.

TOXICOLOGY

Composition data on copolymer trade name mixtures evaluated in toxicity tests are included in Table 6.

Acute Inhalation Toxicity

Styrene/Acrylates Copolymer

In an acute inhalation toxicity study on SunspheresTM Powder, an LC₅₀ of > 5.3 mg/L was reported. The test protocol was not provided.²⁸

An acute inhalation LC₅₀ (4 h) value of > 5.11 mg/L air was reported for ACUDYNETM Shine Polymer and ACUDYNETM Bold Polymer.^{29,30} The test protocol was not described. The animal species was not stated, but it was noted that no clinical signs or mortalities were observed.

1,3-Butadiene and Styrene

Mice and rats were exposed (dynamic flow exposure: 2 h [mice] and 4 h [rats]) to butadiene or styrene vapors.^{26,27} The number, strain, and sex of the animals tested were not specified. LC₅₀ values were: 270 mg/liter (butadiene [mice]), 285 mg/liter (butadiene [rats]), 21 mg/liter (styrene [mice]), and 11.8 mg/liter (styrene [rats]).

Acute Oral Toxicity

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A trade name mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in an acute oral toxicity study.³¹ The mixture was fed in large doses to male and female rats (number of animals not stated). Details relating to the test protocol were not included. The estimated acute oral LD₅₀ was > 5,050 mg/kg (nontoxic). It was noted that this finding was expected because the primary ingredient of the trade name mixture is white mineral oil.

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was evaluated in an acute oral toxicity study involving rats, and an LD₅₀ of > 5 ml/kg was reported. The test protocol was not stated.³²

An oral LD₅₀ of > 2,000 mg/kg body weight (rats) for Syntran® 5903 was reported in a study performed according to OECD guideline n°423.³³ There were no effects on body weight change, and no clinical and behavioral signs or mortalities were observed after dosing. In a toxicological assessment certificate on Syntran® 5907 (another styrene acrylates copolymer trade name material), it was noted that the acute oral toxicity data on Syntran® 5903 can be extrapolated to Syntran® 5907.³⁴ Similarly, in toxicological assessment reports on Syntran® 5904 and Syntran® 5905 it was determined that the acute oral toxicity study results for Syntran® 5903 are applicable to Syntran® 5904 and Syntran® 5905.^{35,36}

Acute Dermal Toxicity

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was evaluated in an acute dermal toxicity study involving rats, and an LD₅₀ of > 5 g/kg was reported. The test protocol was not stated.³²

Repeated Dose Toxicity

Inhalation

Polyacrylate

Polyacrylate, a polymer of acrylic acid and sodium acrylate, was tested in a repeated dose toxicity study involving groups of Fischer 344 rats (ages and number per group not specified).³⁷ It was noted that the large particle size of polyacrylate used in manufacturing makes this material non-respirable, i.e., less than 1% of received material is < 40 microns. The particle size used in this study was reduced (by milling) to make it highly respirable in test animals (mass mean aerodynamic diameter [MMAD] = 1.95 to 2.07 microns). Four groups of animals were exposed to concentrations of 0.05, 0.2, 1, and 10 mg/m³, respectively, 5 days per week (6 h/day) for up to 26 consecutive weeks. The control group was exposed to filtered room air. No adverse effects were observed at concentrations of 0.05 and 0.2 mg/m³. Mild to moderate pulmonary inflammation, which resolved during the recovery period, was observed in the 1.0 mg/m³ exposure group. Exposure to 10 mg/m³ (at this concentration, threshold for clearing inhaled test material from the lungs was exceeded) caused adverse pulmonary effects (marked inflammation and benign alveolar/bronchiolar adenoma) that are not relevant to subthreshold exposure concentrations. Inflammation decreased during the recovery period. The authors stated that these results support the inhalation safety of the polyacrylate material under both occupational and consumer exposure conditions. The 0.05 and 0.2 mg/m³ concentrations were considered no-adverse-effect levels.

Three groups of 120 F344 rats (60 males, 60 females/group) were exposed for 24 months to respirable polyacrylate particles (MMAD ≈ 2 to 3 microns) at concentrations of 0.05, 0.2, and 0.8 mg/m³, respectively.³⁸

Gross necropsy was performed at 6, 12, and 24 months. Gross necropsy results at 24 months indicated no visible effects in males or females exposed to 0.05 mg/m³. Lung nodules were observed in 1 male and 3 females exposed to 0.2 mg/m³. The numbers of pulmonary nodules were even higher in the 0.8 mg/m³ exposure group (7 males and 23 females with nodules). Only one animal (1 female) in the air-exposed control group had a pulmonary nodule. Interim necropsy results at 6 and 12 months indicated the absence of nodule formation in all exposure groups. The authors noted that characterization of the nodules was not possible, and it was determined that conclusions regarding the lung nodule incidence and its significance (if any) in this study could not be made.

Styrene/Acrylates Copolymer

ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were evaluated in a 2-week aerosol (nose only) exposure study involving rats.^{29,30} The test protocol was not stated. There were no signs of clinical toxicity at any administered dose. The no-observed-effect-concentration (NOEC) was 10.8 mg polymer solids/m³, based on slight irritant effects in the lungs at a concentration of 100 mg/m³.

In a 13-week aerosol (nose only) study on ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer involving rats, the no-observable adverse-effect level (NOAEL) for changes in the lung (and related lymph nodes) was 8.3 mg/m³.^{29,30}

Oral

Styrene

The Environmental Protection Agency (EPA) has established a reference dose for chronic oral exposure (RfD) to styrene of 1 mg/kg/day, based on effects on red blood cells and the liver of dogs.³⁹ The RfD is based on the assumption that thresholds exist for certain toxic effects, such as cellular necrosis. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The principal study that served as the basis for the oral RfD is summarized below.

Four beagle dogs/sex were gavaged with doses of 0, 200, 400, or 600 mg styrene/kg bw/day in peanut oil for 560 days.⁴⁰ No adverse effects were observed for dogs administered styrene at 200 mg/kg-day. In the higher dose groups, increased numbers of Heinz bodies in the RBCs, decreased packed cell volume, and sporadic decreases in hemoglobin and RBC counts were observed. Additionally, increased iron deposits and elevated numbers of Heinz bodies were found in the livers. Marked individual variations in blood cell parameters were noted for animals at the same dose. Other parameters examined were body weight, organ weights, urinalyses, and clinical chemistry. The NOAEL in this study was 200 mg/kg-day and the LOAEL was 400 mg/kg-day.

Ocular Irritation

Non-Human

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in an ocular irritation study involving albino rabbits (number of animals not stated).⁴¹ Details relating to the test protocol were not included. The mixture was not a primary ocular irritant in this study. It was noted that, under EPA Guideline No. 81-4, this mixture was “minimally irritating” in rinsed and unrinsed eyes. Additionally, the minimal irritation observed was reversible and the material was assigned to Category IV, EPA’s lowest toxicity category for ocular irritation.

Styrene/Acrylates Copolymer

In the embryonic hen’s egg chorioallantoic membrane (HET-CAM) assay, a 5% dilution of Syntran® 5903 in distilled water was classified as a weak irritant.^{42,33} In this test system, the hen’s egg chorioallantoic membrane

was treated with the test material for 20 seconds and the following endpoints were evaluated: hyperemia, hemorrhage, and coagulation (including opacity and thrombosis).

Sunspheres™ Powder was classified as minimally irritating to the eyes of rabbits.²⁸ The test protocol was not stated.

In an ocular irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-irritant. The test protocol was not stated.³²

Human

1,3-Butadiene

Workers exposed to 1,3-butadiene at concentrations of 8,000 ppm for 8 hours complained of eye irritation and blurred vision.⁴³

In Vitro

Polyacrylate-15, Polyacrylate-18, Polyacrylate-19, and Polyacrylate-21

In the *in vitro* EpiOcular™ ocular irritation screening assay, the following copolymers were classified as non-irritating to the eye: polyacrylate-15 (Syntran® PC 5208),⁴⁴ polyacrylate-18 and polyacrylate-19 mixtures (Syntran® PC 5117 and Syntran® PC 5107),^{45,46} and a product (100.58BM) closely related to polyacrylate-21 (Syntran® PC 5100CG).⁴⁷

Styrene/Acrylates Copolymer

The ocular irritation potential of ACUDYNE™ Shine Polymer was evaluated in the bovine corneal opacity and permeability test *in vitro*. The test protocol was not stated. Results were negative.²⁹

ACUDYNE™ Bold Polymer was classified as a non-irritant in the bovine corneal opacity and permeability test *in vitro*.³⁰ The test protocol was not stated.

Skin Irritation and Sensitization

Non-Human

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in a skin irritation study involving albino rabbits (number of animals not stated).⁴⁸ Details relating to the test protocol were not included. The material was not a primary skin irritant in this study. It was noted that the descriptive rating (under EPA Guideline No. 81-5) for this mixture was “slightly irritating”, the lowest descriptive rating possible. Additionally, because this slight irritation was reversible, the trade name material was assigned to the EPA’s lowest toxicity category (Category IV) for dermal irritation.

Styrene/Acrylates Copolymer

In a skin irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-irritant. The test protocol was not stated.³²

The skin irritation potential of ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer was evaluated in the EpiDermal *in vitro* assay.^{29,30} The test protocol was not stated. Results were negative.

Styrene/Acrylates Copolymer and Polystyrene

Syntran® 5903 (undiluted) was classified as a non-sensitizer in a guinea pig sensitization test, performed according to OECD guideline n°406.^{42,33} Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-sensitizers.^{42,35,34,36}

ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were classified as non-sensitizers in the mouse local lymph node assay.^{29,30} The test protocol was not stated.

Styrene and Methylstyrene

The skin sensitization potential of styrene was evaluated in the guinea pig maximization test (15 guinea pigs).⁴⁹ Details relating to the test protocol were not included. The test procedure involved intradermal injections of 10% (w/v) styrene, topical application of 20% (w/v) styrene, and challenge with 2% (w/v) styrene in acetone. Skin sensitization was not observed in any of the animals tested. Methylstyrene was also evaluated in a maximization test involving 15 guinea pigs, and the procedure involved intradermal injections of 2.5% (w/v) methylstyrene, topical application of 5% (w/v) methylstyrene, and challenge with 0.5% (w/v) methylstyrene in acetone. The results were also negative.

Human

Styrene/Acrylates Copolymer and Polystyrene

Syntran® 5903 (5% in distilled water) was classified as having good skin compatibility in 10 volunteers patch tested (single application patch test). Study details were not provided.^{42,33} No signs of irritation were recorded, and observations throughout the test interval were within normal limits. Based on these results for Syntran® 5903, Syntran® 5904 (another styrene acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-irritants.^{42,35,34,36}

Styrene/Acrylates Copolymer

In a 21-day cumulative skin irritation study, OPULYN™ 302B Opacifier was classified as non-irritating and non-sensitizing. The test protocol was not stated.³²

OPULYN™ 301 Opacifier was also classified as non-irritating and non-sensitizing in a 21-day cumulative irritation study. The test protocol was not stated.⁵⁰

Styrene and Methylstyrene

Styrene (5% w/v in petrolatum) was evaluated in a skin sensitization study involving 303 patients (diagnoses not stated).⁴⁹ Details relating to the test procedure were not provided. Negative results were reported for all patients. Negative results for methylstyrene (1% w/v in ethanol) in these patients were also reported.

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in a human repeated insult patch test involving 117 subjects.⁵¹ Details relating to the test protocol were not included. The subjects were evaluated for redness, swelling, “flares” and itching. The mixture did not induce allergic contact dermatitis in any of the subjects. It was noted that this conclusion was confirmed by a board-certified dermatologist.

In Vitro

Styrene/Acrylates Copolymer and Polystyrene

In the embryonic hen's egg chorioallantoic membrane (HET-CAM) assay, a 5% dilution of Syntran® 5903 in distilled water was classified as a weak irritant.^{42,33} In this test system, the hen's egg chorioallantoic membrane was treated with the test material for 20 seconds and the following endpoints were evaluated: hyperemia, hemorrhage, and coagulation (including opacity and thrombosis). Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were also classified as weakly irritating to the chorioallantoic membrane.^{42,35,34,36} Based on the minimal irritation potential of Syntran® 5903 in the HET-CAM assay (generally used to evaluate ocular irritation potential), it was concluded that it is not likely that this trade name material, or the other trade name materials, would produce dermal irritation.

Polyacrylate-15, Polyacrylate-18, Polyacrylate-19, and Polyacrylate-21

Based on negative results in the *in vitro* EpiOcular™ ocular irritation screening assay (see Ocular Irritation section), it is expected that the following copolymers would not produce dermal irritation: polyacrylate-15 (Syntran® PC 5208),⁴⁴ polyacrylate-18 and polyacrylate-19 mixtures (Syntran® PC 5117 and Syntran® PC 5107),^{45,46} and a product (100.58BM) closely related to polyacrylate-21 (Syntran® PC 5100CG).⁴⁷

Polyacrylate-15

In a cosmetic ingredient safety dossier on Syntran® PC 5208, skin irritation data on this trade name material were not included.⁴⁴ However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on Syntran® PC 5208 indicates that this trade name material is not likely to produce skin sensitization, since skin is less susceptible to irritation than eye tissue.

Polyacrylate-18 and Polyacrylate-19 (mixture)

Skin irritation data were not included in a cosmetic ingredient safety dossier on polyacrylate-18 and polyacrylate-19 (Syntran® PC 5117).⁴⁵ However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on a closely related product (Syntran® 5100, composition not stated) indicates that Syntran® PC 5117 is not likely to produce dermal sensitization, since skin is less susceptible to irritation than eye tissue. These statements are also applicable to Syntran® PC 5107 (polyacrylate-18 and polyacrylate-19).⁴⁶

Polyacrylate-21

In a cosmetic ingredient safety dossier on polyacrylate-21 (Syntran® PC 5100CG), skin irritation data on this trade name material were not included.⁴⁷ However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on a closely related product (100.58BM, composition data not provided) indicates that Syntran® PC 5100CG is not likely to produce dermal sensitization, since skin is less susceptible to irritation than eye tissue.

Case Reports

Styrene and Methylstyrene

A 40-year-old man with a history of bronchitis and contact allergy to styrene cross-reacted when patch-tested with 3- and 4-vinytoluene (also known as 3- and 4-methylstyrene, respectively).⁴⁹ The vinyltoluene compounds were patch-tested at concentrations equimolar to 0.1% w/v styrene. The patient also had a positive reaction to styrene (0.1% and 5% v/v in methylethyl ketone).

In a subsequent case report, the same patient cross-reacted when patch tested with 2-, 3-, and 4-vinyltoluene (2-, 3-, and 4-methylstyrene, respectively) and to the metabolites styrene epoxide and 4-vinylphenol (4-hydroxystyrene).⁵² It is assumed that styrene is a prohapten metabolized in the skin by aryl hydrocarbon hydroxylase (AHH) to styrene epoxide, which acts as a true hapten.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Styrene

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel concluded that styrene does not cause developmental or reproductive toxicity in experimental animals.⁵³ In developmental toxicity studies in rats and rabbits, the highest exposure concentration/dose on gestation days 6-15 (600 ppm by inhalation or 300 mg/kg body weight/day by oral dosing) did not have any observable adverse effects on fetuses. Rats and rabbits were used in inhalation studies, and rats only were involved in the oral dosing study. The effects of styrene exposure on reproduction and post-natal development were assessed in 2 multigeneration studies involving rats. Neither study produced results indicating a styrene-induced reproductive effect, even at the highest concentrations administered. However, in one of the studies, there was decreased birth weight and delays in the postnatal development of pups from parents exposed (by inhalation) to 500 ppm styrene from 70 days prior to mating through gestation day 20. This concentration of styrene also caused a significantly reduced body weight gain in the dams. Thus, the NTP-CERHR Expert Panel concluded that it was not possible to separate the observed effects in the offspring from the effects on maternal weight. Inhalation exposure to 500 ppm styrene did not cause developmental neurotoxicity.

In the second multigeneration study, a subset of animals (COBS (SD) BR rats) from a 2-year chronic toxicity study in which styrene was administered at concentrations up to 250 ppm in drinking water (estimated intake = 18 mg/kg body weight/day (for males) and 23 mg/kg body weight/day (for females) were used. The parental generations were cohabited after 90 days on study. Results indicated no treatment-related effects on maternal food consumption or weight gain, and no significant developmental effects on the pups. The NTP-CERHR Expert Panel considered these data to be relevant for the assessment of potential human hazard.

The NTP-CERHR Expert Panel determined that there was insufficient information available to arrive at conclusions about reproductive and developmental outcomes from studies of humans exposed to styrene. Studies performed in occupational settings suggest that the exposure of women to styrene is associated with slightly increased levels of prolactin in blood serum and possible depletion of peripheral blood dopamine metabolizing activities, when compared to levels in women not occupationally exposed to styrene. The Panel determined that the clinical relevance of these effects is uncertain for the following 2 reasons: (1) the average elevation in prolactin concentrations in blood serum was small and within the normal range of blood serum values and (2) menstrual function and other reproductive endpoints were not evaluated in these studies.⁵³

1,3-Butadiene

The following reproductive toxicity study summaries are included in the 1984 NTP report on the toxicology and carcinogenesis of 1,3-butadiene.²⁶ The fertility of rats was not severely impaired when they were exposed (via inhalation) to 1,3-butadiene at concentrations of 600-6,700 ppm for 7.5 hours per day, 6 days per week, for 8 months; however, the decreased fecundity observed may have been related to exposure. No evidence of degenerative testicular changes in males was seen, and all embryos appeared normal at necropsy.

When female rats were exposed (via inhalation) to 1,3-butadiene for 4 months at 45 ppm, increased embryonic mortality and teratogenesis were reported.

Pregnant female Sprague-Dawley rats exposed (via inhalation) to 1,3-butadiene at concentrations of 0, 200, 1,000, or 8,000 ppm for 6 hours per day during days 6-15 of gestation showed embryonic growth retardation and slight embryo-mortality at all concentrations. At the highest exposure concentration, evidence of teratogenicity (major fetal defects such as cardiovascular, sternebral, and thoracic abnormalities) was seen.²⁶

GENOTOXICITY

Styrene/Acrylates Copolymer and Polystyrene

In the Ames test (OECD guideline n°471), Syntran® 5903 (doses up to 5,000 µg/plate) was non-genotoxic with and without metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and in *Escherichia coli* strains WP2, pKM101, and uvr A.^{42,33} Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-genotoxic.^{42,35,34,36}

The genotoxicity of polystyrene was evaluated in the Ames test using the following *Salmonella typhimurium* strains, with and without metabolic activation: TA97, TA98, TA100, and TA1535.⁵⁴ Concentrations of the test substance were not stated; however, at least 5 concentrations were tested. Methyl ethyl ketone served as the vehicle and the control. Polystyrene was not genotoxic with or without metabolic activation in any of the bacterial strains tested. The positive controls in experiments without metabolic activation were: 2-nitrofluorene, 4-nitro-o-phenylenediamine, sodium azide, 9-aminoacridine, mitomycin C, and methyl methanesulfonate. The positive control for the metabolic activation experiments was 2-aminoanthracene. Results for the vehicle control or positive controls were not stated.

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was not genotoxic in the Ames test, with or without metabolic activation. The test protocol was not stated.³² This trade name material also was not genotoxic in the *in vitro* cytogenetic assay, with or without metabolic activation (test protocol not stated).

In the Ames test, ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were not genotoxic.^{29,30} Negative results were also reported for these 2 trade name materials in the chromosomal aberrations test *in vitro* (test protocol not stated).

OPULYN™ 301 Opacifier was not genotoxic in the Ames test, with or without metabolic activation.⁵⁰ This trade name material also was not genotoxic in the *in vitro* cytogenetic assay, with or without metabolic activation (test protocol was not stated.).

Polyacrylate-18 and Polyacrylate-19 (mixture)

Syntran® PC 5117 (polyacrylate-18 and polyacrylate-19) was evaluated for genotoxicity in the Ames test at doses up to 5,000 µg/plate using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2 uvrA. Results were negative with and without metabolic activation.⁴⁵ These statements are also applicable to Syntran® PC 5107 (polyacrylate-18 and polyacrylate-19).⁴⁶

Polyacrylate-21

Syntran® PC 5100 (mixture of polyacrylate-21 and acrylates/dimethylaminoethyl methacrylate copolymer)² was evaluated for genotoxicity in the Ames test at doses up to 5,000 µg/plate using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2 uvrA. Results were negative with and without metabolic activation.⁴⁷ Genotoxicity data on polyacrylate-21 (Syntran® 5100CG) were not provided, and data on a closely related product (Syntran® PC 5100) were used to evaluate the genotoxicity of Syntran® 5100CG. It was noted that negative results would be expected for Syntran® 5100CG.

Polyacrylate

The genotoxicity of polyacrylate (polymer of acrylic acid and sodium acrylate) was evaluated in the following assays:³⁷ unscheduled DNA synthesis assay (rat hepatocytes), the mouse lymphoma mammalian cell

assay, and the *in vivo* cytogenetics assay (rat bone marrow cells). Neither the test concentrations nor details relating to the test protocols were stated. However, it was stated that polyacrylate was not genotoxic in any of the assays.

CARCINOGENICITY

Information relating to the carcinogenicity of styrene and vinyl-type styrene copolymers and component monomers is presented in Table 8. Particularly, 1,3-butadiene and styrene monomer components have been classified as carcinogenic. In addition to the information presented in Table 8, a committee of the National Research Council (NRC) conducted a scientific peer review of the styrene assessment presented in the *12th Report on Carcinogens* (RoC). The committee found that the overall conclusion reached by the NTP in 2011, that styrene is “reasonably anticipated to be a human carcinogen”, is appropriate.⁵⁵

It should be noted that polyacrylates are included on the 2013 list of substances that have been nominated to the NTP’s *Report on Carcinogens* (RoC), but have not yet been approved for formal review.⁵⁶

OTHER EFFECTS

Hormonal Activity

Polystyrene

The estrogenic (uterotrophic) activity of low molecular weight polystyrene (identified as F2L5250) was studied in the Tiecco test using groups of 10 weanling female Wistar outbred rats (HsdCpb:WU strain).⁵⁷ The test substance was fed to 5 groups at the following dietary concentrations, respectively, during a 4-day period: 10 ppm, 20 ppm, 40 ppm, 80 ppm, and 160 ppm. The control group was fed standard diet only. Diethylstilbesterol (DES) served as the positive control. The mean absolute and relative uterine weights of the treatment groups were used for qualitative and quantitative assessment of possible uterotrophic activity. There were no significant differences in mean absolute and relative uterus weights between the control group and the 10 ppm, 20 ppm, 40 ppm, or 80 ppm group. However, significant and dose-related increases in mean absolute and relative uterus weights were observed in the 160 ppm group and in groups fed 5 ppb, 10 ppb, and 20 ppb DES, respectively. The results of this study indicated that the highest no-effect-level for estrogenic activity was 80 ppm polystyrene in the diet, which corresponded to a daily intake of 13.3 mg polystyrene/kg body weight. It was noted that 100 ppm polystyrene induced the same level of estrogenic activity as 5 ppb DES. It was concluded that the potency (estrogenic activity) of low molecular weight polystyrene (F2L5250) was a factor of 20,000 less than that of DES.

SUMMARY

The safety of 35 styrene and vinyl-type styrene copolymers as used in cosmetics is evaluated in this safety assessment. These ingredients function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products. Very limited safety test data on the styrene and vinyl-type styrene copolymers reviewed in this safety assessment were found in the published literature. However, data on monomers, styrene and 1,3-butadiene, are included.

Information on the use of these ingredients as a function of product type was obtained from FDA’s VCRP in 2014. The highest use frequency was reported for ethylene/propylene/styrene copolymer, followed by butylene/ethylene/styrene copolymer. The Personal Care Products Council conducted a survey of ingredient use concentrations in 2013-2014, and maximum use concentrations ranging from 0.000038% (styrene/VP copolymer) to 36.5% (polystyrene) were reported. The highest maximum reported use concentrations for rinse-off and leave-on products were 36.5% (polystyrene) and 35% (styrene/acrylates copolymer), respectively.

Data provided by industry indicate that styrene and vinyl-type styrene copolymer trade name materials contain styrene monomer at levels of < 100 ppm or less.

The absorption of styrene was low (averaging 1 $\mu\text{g}/\text{cm}^2/\text{minute}$) in human volunteers exposed by placing one hand in liquid styrene for 10 to 30 minutes. The percutaneous absorption of styrene was not an important contribution to the body burden in a field study comparing the urinary excretion of styrene metabolites in 4 groups of workers, all performing the same task, but wearing different protective equipment. It was concluded that the percutaneous absorption of styrene was not an important contribution to the body burden. Styrene is primarily metabolized to styrene 7,8-oxide by cytochrome P450 enzymes.

Nine minutes after rabbits were exposed to 1,3-butadiene at concentrations of 250,000 ppm, the test chemical was found in the femoral artery at a concentration of 0.26 mg/ml and in the femoral vein at a concentration of 0.18 mg/ml. Following 1 h of exposure to 130,000 ppm 1,3-butadiene in rats, the chemical was detected in the brain and liver. At 2 h post-exposure to the same concentration (rats), 1,3-butadiene was detected in the perirenal fat, liver, brain, spleen, and kidneys. The first step in butadiene metabolism involves cytochrome P450-mediated oxidation to epoxybutene.

Polyacrylate, a polymer of acrylic acid and sodium acrylate, was tested in a repeated dose inhalation toxicity study involving groups of Fischer 344 rats. The particle size (MMAD) used in this study was 1.95 to 2.07 microns. The animals were exposed to polyacrylate at concentrations of 0.05, 0.2, 1, and 10 mg/m^3 . Mild to moderate pulmonary inflammation and benign alveolar/bronchiolar adenomas were reported, and the 0.05 and 0.2 mg/m^3 concentrations were considered no-adverse-effect levels.

The EPA has estimated the safe dose of styrene for human oral exposure during a lifetime to be 1 mg/kg-day.

Workers exposed to 1,3-butadiene at concentrations of 8,000 ppm for 8 hours complained of eye irritation and blurred vision.

In the maximization test, sensitization was not observed in 15 guinea pigs challenged with 2% (w/v) styrene in acetone. Results were also negative for sensitization in 303 patients tested with 5% (w/v) styrene in petrolatum.

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel concluded that styrene does not cause developmental or reproductive toxicity in experimental animals. The highest doses/exposure concentrations in developmental toxicity studies (rats and rabbits) evaluated were 600 ppm (inhalation) or 300 mg/kg body weight/day by oral dosing. The NTP-CERHR Expert Panel determined that there was insufficient information available to arrive at conclusions on reproductive and developmental outcomes from studies of humans exposed (occupational exposure) to styrene.

The fertility of rats was not severely impaired when they were exposed to 1,3-butadiene at concentrations of 600-6,700 ppm for 8 months (6 days/week). However, it was noted that the decreased fecundity observed may have been exposure-related. There was no evidence of degenerative testicular changes in males. The results of other studies indicated increased embryonic mortality and teratogenesis at exposure concentrations as low as 45 ppm (4-month exposure) and embryonic growth retardation and embryo mortality at exposure concentrations ranging from 200 ppm to 8,000 ppm. Teratogenicity was observed only at the highest concentration of 8,000 ppm.

Polystyrene was not genotoxic with or without metabolic activation in the Ames test. Polyacrylates were not genotoxic in the following tests: Ames test, unscheduled DNA synthesis assay (rat hepatocytes), mouse lymphoma mammalian cell assay, and the *in vivo* cytogenetics assay (rat bone marrow cells).

The subcutaneous implantation of various physical forms of polystyrene produced sarcomas in rats. In an NTP oral carcinogenicity bioassay on styrene, it was concluded that there was no convincing evidence of carcinogenicity in rats or mice receiving doses up to 2,000 mg/kg for 78 or 103 weeks (rats) or 78 weeks (mice). However, the NTP has concluded that styrene is reasonably anticipated to be a human carcinogen based on the results of occupational cohort studies. The EPA and IARC have also classified styrene as possibly carcinogenic to

humans. A committee of the NRC conducted a scientific peer review of the styrene assessment presented in the NTP 12th Report on Carcinogens, and concluded that the overall conclusion reached by the NTP is appropriate.

In NTP inhalation carcinogenicity studies, 1,3-butadiene was carcinogenic in B6C3F₁ mice at concentrations ≥ 20 ppm (male mice) and ≥ 6.25 ppm (female mice). Inhalation exposure was also associated with non-neoplastic lesions in the respiratory epithelium, liver necrosis, and testicular or ovarian atrophy. It should be noted that EPA and IARC have concluded that 1,3-butadiene is carcinogenic in humans by inhalation exposure.

The IARC has determined that epidemiological information on styrene-butadiene copolymer workers, which indicates lymphato-hematopoietic malignancies, clearly requires elucidation by further studies.

A cross-sectional respiratory survey of workers (164 workers: 153 men, 11 women; average age = 28.4 years) exposed to polyacrylate dust was performed to assess possible respiratory effects. There was no evidence of an excess risk of lung cancer or chest x-ray abnormalities in exposed workers. However, there were exposure-related decrements in lung function.

Polyacrylates are included on the 2013 list of substances that have been nominated to the NTP's *Report on Carcinogens*, but have not yet been approved for formal review.

With certain exceptions, results were negative in the following toxicity tests on styrene and vinyl-type styrene copolymers reviewed in this safety assessment: acute inhalation, acute oral, acute dermal, ocular irritation, skin irritation, skin sensitization, and genotoxicity. The exceptions include: In an *in vitro* skin irritation test, styrene/acrylates copolymer (Syntran® PC5903) was classified as a weak irritant. Styrene/acrylates copolymer (Sunspheres™ powder) was minimally irritating to the eyes of rabbits. In a 2-week aerosol (nose-only) study on 2 styrene/acrylates copolymer trade name materials (Acudyne™ Bold Polymer and Acudyne™ Shine Polymer), a slight irritant effect on the lungs was noted at a concentration of 100 mg/m³. In light of these findings, it should be noted that a 13-week aerosol (nose-only) study on these 2 trade name materials yielded an NOAEL of 8.3 mg/m³.

Low molecular weight polystyrene was found to have estrogenic (uterotrophic) activity in rats fed a dietary concentration of 160 ppm during a 4-day period.

DISCUSSION

After considering the large sizes of these molecules, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of toxicity tests provided the Panel with a sufficient basis to assess the safety of these polymers as used in cosmetics. Styrene monomer, a component of all of the copolymers reviewed in this safety assessment, and 1,3-butadiene monomer are classified as carcinogenic in animals and in humans. Taking into consideration ingredient use concentrations and the data on residual monomer content, the Panel agreed that levels of residual styrene or 1,3-butadiene in cosmetic products would be substantially below levels of concern.

The Panel also discussed the potential for incidental inhalation exposures to these ingredients in products that are sprayed or in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone, ingredient use concentrations, and negative results in toxicity tests, incidental inhalation would not lead to local respiratory effects or systemic effects.

CONCLUSION

The CIR Expert Panel concluded that the following 35 ingredients are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment.

Ethylene/Propylene/Styrene Copolymer
 Butylene/Ethylene/Styrene Copolymer
 Acrylates/Ethylhexyl Acrylate/Styrene Copolymer*
 Butyl Acrylate/Styrene Copolymer
 C4-6 Olefin/Styrene Copolymer*
 C5-6 Olefin/Styrene Copolymer*
 Hydrogenated Butadiene/Isoprene/Styrene
 Copolymer*
 Hydrogenated Butylene/Ethylene/Styrene Copolymer
 Hydrogenated Ethylene/ Propylene/Styrene
 Copolymer
 Hydrogenated Styrene/Butadiene Copolymer
 Hydrogenated Styrene/Isoprene Copolymer
 Isobutylene/Styrene Copolymer
 Methacrylic Acid/Styrene/VP Copolymer*
 Methylstyrene/Vinyltoluene Copolymer
 Polystyrene
 Polystyrene/Hydrogenated Polyisopentene
 Copolymer
 Sodium Methacrylate/Styrene Copolymer*

Sodium Styrene/Acrylates Copolymer
 Sodium Styrene/Acrylates/Ethylhexyl
 Acrylate/Lauryl Acrylate Copolymer*
 Styrene/Acrylates Copolymer
 Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl
 Acrylate Copolymer*
 Styrene/Butadiene Copolymer
 Styrene/Isoprene Copolymer*
 Styrene/Methylstyrene Copolymer*
 Styrene/Stearyl Methacrylate Crosspolymer*
 Styrene/VA Copolymer*
 Styrene/VP Copolymer
 Polyacrylate-2*
 Polyacrylate-5
 Polyacrylate-12*
 Polyacrylate-15
 Polyacrylate-16
 Polyacrylate-18*
 Polyacrylate-21
 Polyacrylate-30*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

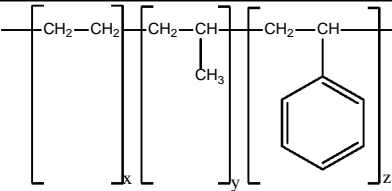
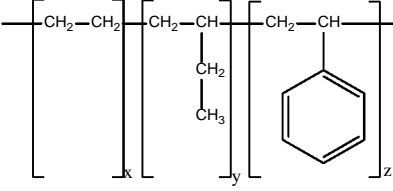
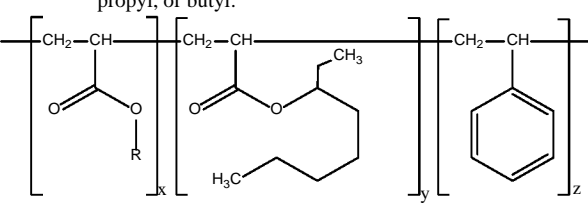
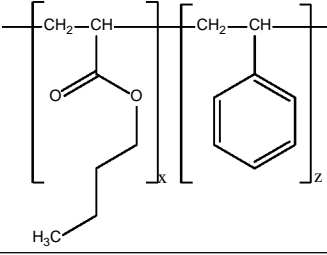
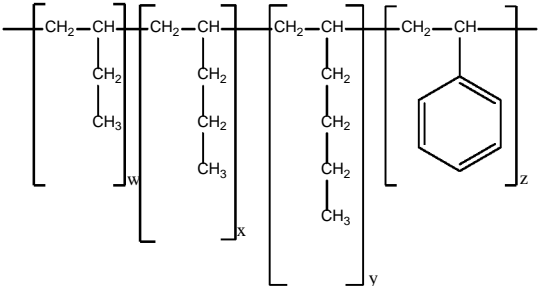
| Ingredient CAS No. | Definition | | Function(s) |
|--|---|--|---------------------------------------|
| Ethylene/Propylene/Styrene Copolymer 68648-89-5 | Ethylene/Propylene/Styrene Copolymer is a polymer of ethylene, propylene and styrene monomers that has been terminated by hydrogenation. |  | Viscosity increasing agent-nonaqueous |
| Butylene/Ethylene/Styrene Copolymer 66070-58-4 | Butylene/Ethylene/Styrene Copolymer is a polymer of butylene, ethylene and styrene monomers terminated by hydrogenation. |  | Viscosity increasing agent-nonaqueous |
| Acrylates/Ethylhexyl Acrylate/Styrene Copolymer | Acrylates/Ethylhexyl Acrylate/Styrene Copolymer is a copolymer of ethylhexyl acrylate, styrene and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters. wherein R is hydrogen, methyl, ethyl, propyl, or butyl. |  | Film formers |
| Butyl Acrylate/Styrene Copolymer | Butyl Acrylate/Styrene Copolymer is a copolymer of butyl acrylate and styrene monomers. |  | Film formers |
| C4-6 Olefin/Styrene Copolymer | C4-6 Olefin/Styrene Copolymer is a copolymer of C4-6 olefins and styrene monomers. |  | Epilating agents |

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

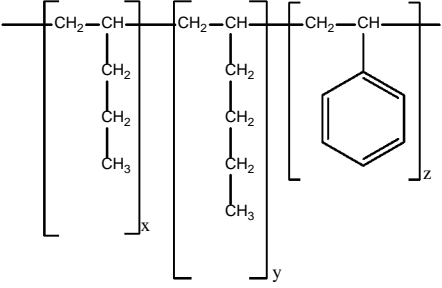
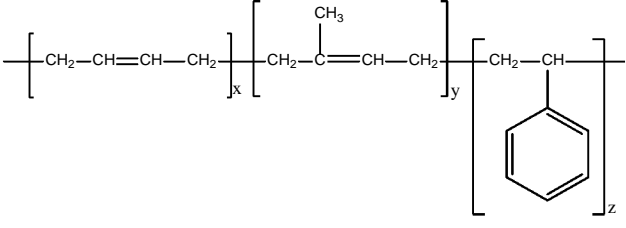




| Ingredient CAS No. | Definition | Function(s) |
|---|---|--|
| C5-6 Olefin/Styrene Copolymer | C5-6 Olefin/Styrene Copolymer is the copolymer of C5-6 olefins and styrene monomers. | Epilating agents |
| |  | |
| Hydrogenated Butadiene/Isoprene/Styrene Copolymer 132778-07-5 | Hydrogenated Butadiene/Isoprene/Styrene Copolymer is the end-product of the controlled hydrogenation of a block copolymer composed of 1,3-butadiene, isoprene and styrene monomers. | Film formers |
| |  | |
| Hydrogenated Butylene/Ethylene/Styrene Copolymer | Hydrogenated Butylene/Ethylene/Styrene Copolymer is a polymer of butylene, ethylene and styrene that has been hydrogenated. | Viscosity increasing agents-nonaqueous |
| |  | |
| Hydrogenated Ethylene/Propylene/Styrene Copolymer | Hydrogenated Ethylene/Propylene/Styrene Copolymer is a polymer of ethylene, propylene and styrene that has been hydrogenated. | Viscosity increasing agents-nonaqueous |
| |  | |
| Hydrogenated Styrene/Butadiene Copolymer 66070-58-4 | Hydrogenated Styrene/Butadiene Copolymer is the hydrogenated polymer of styrene and 1,4-butadiene. | Film formers; viscosity increasing agents-nonaqueous |
| |  | |
| Hydrogenated Styrene/Isoprene Copolymer 68648-89-5 | Hydrogenated Styrene/Isoprene Copolymer is the end product of the controlled hydrogenation of Styrene/Isoprene Copolymer. | Viscosity increasing agents-nonaqueous |
| |  | |

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

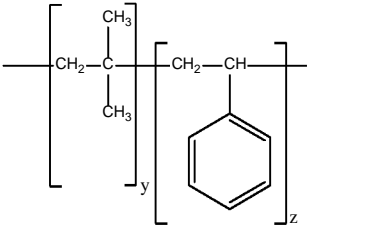
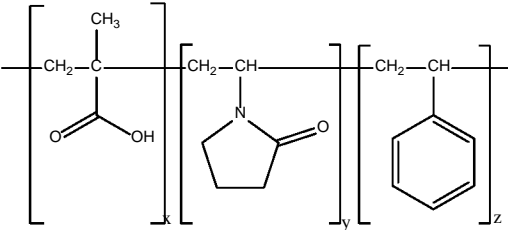
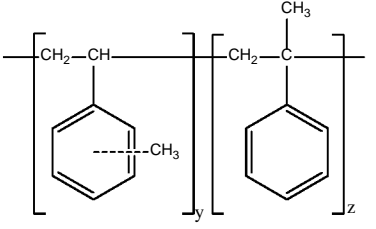
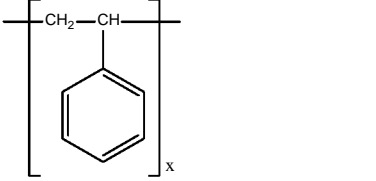
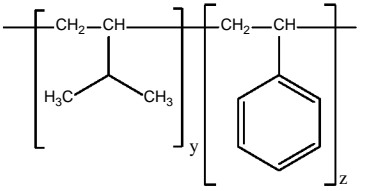
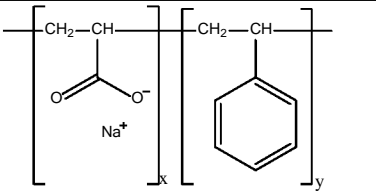
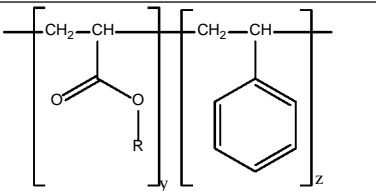
| Ingredient CAS No. | Definition | | Function(s) |
|---|---|---|--|
| Isobutylene/Styrene Copolymer 9011-12-5 | Isobutylene/Styrene Copolymer is a copolymer of isobutylene and styrene monomers. |  | Film formers |
| Methacrylic Acid/Styrene/VP Copolymer 27554-92-3 | Methacrylic Acid/Styrene/VP Copolymer is a copolymer of styrene, methacrylic acid and vinyl pyrrolidone. |  | Opacifying agents |
| Methylstyrene/Vinyltoluene Copolymer 9017-27-0 | Methylstyrene/Vinyltoluene Copolymer is the polymer of methylstyrene and vinyltoluene monomers. |  | Viscosity increasing agents-nonaqueous |
| Polystyrene 9003-53-6 | Polystyrene is the polymer that conforms to the formula. <i>Polystyrene is the homopolymer formed from the polymerization of vinylbenzene.</i> |  | Film formers; viscosity increasing agents-nonaqueous |
| Polystyrene/Hydrogenated Polyisopentene Copolymer | Polystyrene/Hydrogenated Polyisopentene Copolymer is a copolymer of polystyrene and hydrogenated polyisopentene. |  | Not reported |
| Sodium Methacrylate/Styrene Copolymer 33970-45-5 | Sodium Methacrylate/Styrene Copolymer is a copolymer of sodium methacrylate and styrene monomers. |  | Opacifying agents |
| Sodium Styrene/Acrylates Copolymer 9010-92-8 | Sodium Styrene/Acrylates Copolymer is the sodium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters. |  <p data-bbox="786 1829 1159 1898">wherein R is a lone pair of electrons with a sodium cation, methyl, ethyl, propyl, or butyl.</p> | Film formers; viscosity increasing agents-aqueous |

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

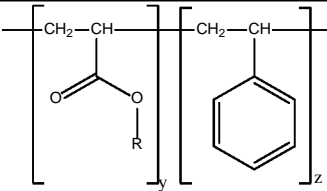
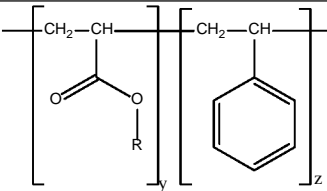
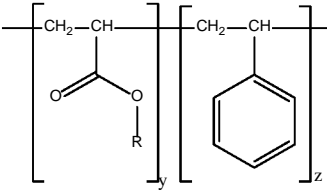
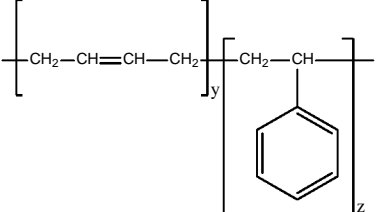
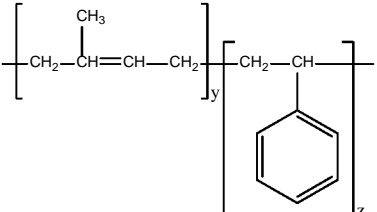
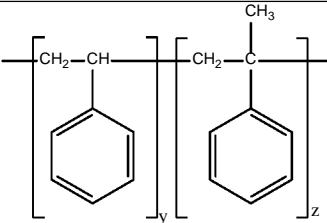
| Ingredient CAS No. | Definition | | Function(s) |
|--|--|--|---------------------------------|
| Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer | Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer is the sodium salt of Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer |  <p>wherein R is a lone pair of electrons with a sodium cation, methyl, ethyl, propyl, butyl, lauryl, or ethylhexyl.</p> | Film formers |
| Styrene/Acrylates Copolymer 25034-86-0 25085-34-1 9010-92-8 | Styrene/Acrylates Copolymer is a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters. |  <p>wherein R is hydrogen, methyl, ethyl, propyl, or butyl.</p> | Film formers; opacifying agents |
| Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer | Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer is a copolymer of styrene, acrylates, ethylhexyl acrylate and lauryl acrylate. |  <p>wherein R is a hydrogen, methyl, ethyl, propyl, butyl, lauryl, or ethylhexyl.</p> | Film formers |
| Styrene/Butadiene Copolymer 9003-55-8 | Styrene/Butadiene Copolymer is a copolymer of styrene and butadiene monomers. |  | Opacifying agents |
| Styrene/Isoprene Copolymer 25038-32-8 | Styrene/Isoprene Copolymer is a copolymer of styrene and isoprene monomers. |  | Film formers; opacifying agents |
| Styrene/Methylstyrene Copolymer 37218-15-8 9011-11-4 | Styrene/Methylstyrene Copolymer is a copolymer of styrene and methyl styrene monomers. |  | Binders; epilating agents |

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

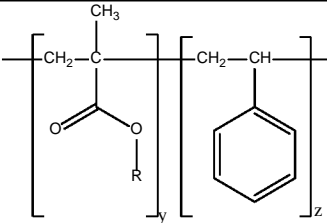
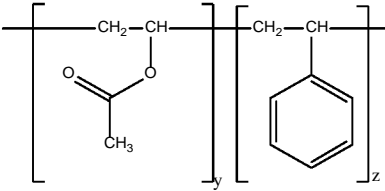
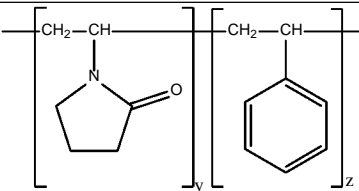
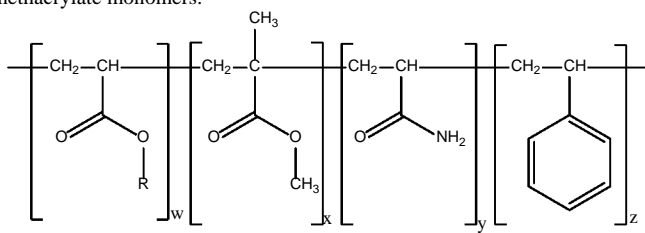
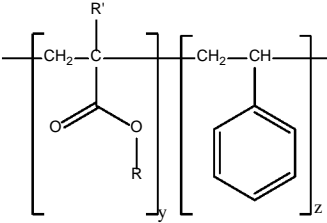
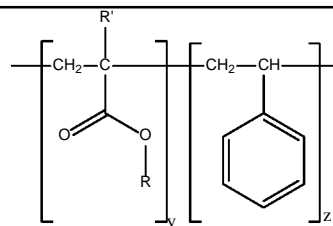
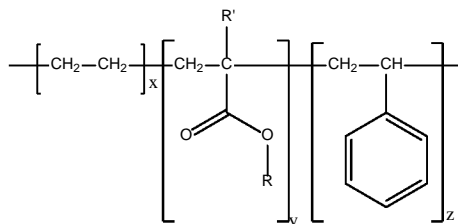
| Ingredient CAS No. | Definition | | Function(s) |
|---|--|--|--|
| Styrene/Stearyl Methacrylate Crosspolymer 91838-84-5 | Styrene/Stearyl Methacrylate Crosspolymer is a copolymer of styrene and stearyl methacrylate monomers crosslinked with divinylbenzene. |  <p>wherein R is an eighteen carbon, saturated alkyl chain</p> | Absorbents; skin-conditioning agents-miscellaneous |
| Styrene/VA Copolymer | Styrene/VA Copolymer is a copolymer of styrene and vinyl acetate monomers. |  | Film formers; opacifying agents |
| Styrene/VP Copolymer 25086-29-7 | Styrene/VP Copolymer is a copolymer prepared from vinylpyrrolidone and styrene monomers. |  | Film formers |
| Polyacrylate-2 31759-42-9 | Polyacrylate-2 is a copolymer of styrene, acrylamide, octyl acrylate and methyl methacrylate monomers. |  | Film formers |
| Polyacrylate-5 | Polyacrylate-5 is a copolymer of styrene, ethylhexyl acrylate, hydroxyethyl acrylate, and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters. |  <p>wherein R is a hydrogen, methyl, ethyl, propyl, butyl, hydroxyethyl, or ethylhexyl. wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, ethyl, propyl, or butyl, R' may also be methyl.</p> | Film formers |

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

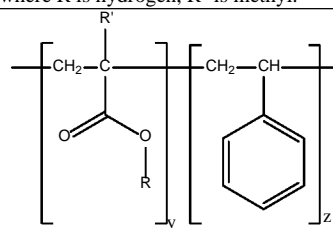
| Ingredient CAS No. | Definition | Function(s) |
|-------------------------------|---|--|
| Polyacrylate-12 | Polyacrylate-12 is a copolymer of C3-11 acrylate, styrene, methacrylic Acid and acetoacetoxyethyl methacrylate monomers. | Film formers; nail conditioning agents |
| Polyacrylate-15 67892-91-5 | Polyacrylate-15 is a copolymer of n-butyl acrylate, ethyl acrylate, methyl methacrylate, ethylene, methacrylic acid and styrene monomers | Film formers; hair fixatives |
| Polyacrylate-16 67952-78-7 | Polyacrylate-16 is a copolymer of n-butyl acrylate, diethylaminoethyl methacrylate, ethyl acrylate, methacrylic acid, hydroxypropyl methacrylate, methyl methacrylate and styrene monomers. | Film formers; hair fixatives |
| Polyacrylate-18 | Polyacrylate-18 is a copolymer of n-butyl acrylate, ethyl acrylate, methacrylic acid, hydroxypropyl methacrylate and styrene monomers, | Film formers; hair fixatives |



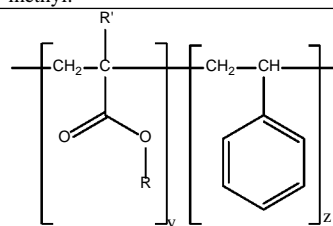
wherein R is a hydrogen, methyl, an alkyl chain from 3 to 11 carbons in length methyl, or acetoacetoxyethyl
wherein R' is hydrogen, or in the cases where R is methyl, or acetoacetoxyethyl, R' is methyl.



wherein R is a hydrogen, methyl, ethyl, or butyl wherein R' is hydrogen, or in the case where R is hydrogen, R' is methyl.



wherein R is a hydrogen, methyl, diethylaminoethyl, or hydroxypropyl
wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, diethylaminoethyl, or hydroxypropyl, R' is methyl.



wherein R is a hydrogen, ethyl, butyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, butyl, or hydroxypropyl, R' is methyl.

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

| Ingredient CAS No. | Definition | Function(s) |
|--------------------|---|--|
| Polyacrylate-21 | <p>Polyacrylate-21 is a copolymer of 2-ethylhexyl acrylate, butyl methacrylate, methacrylic acid, methyl methacrylate, hydroxypropyl methacrylate and styrene.</p> | <p>Binders; film formers; hair fixatives</p> |
| Polyacrylate-30 | <p>Polyacrylate-30 is a copolymer of acrylonitrile, methacrylic acid, octyl acrylate, and styrene. wherein R is a hydrogen, methyl, butyl, ethylhexyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, butyl, or hydroxypropyl, R' is methyl. wherein R is an octyl chain</p> | <p>Nail conditioning agents</p> |

Table 2. Properties of Polystyrene.^{58,4,5}

| | |
|----------------------------------|--|
| Form | Transparent, hard solid; water-clear solid plastic |
| Molecular Mass | 10,000 to 300,000 |
| Density | 1.04-1.065 (amorphous); 1.111 (crystalline) |
| Stability | Yellows on exposure to light |
| Solubility | Soluble in ethylbenzene, methyl isobutyl ketone, tetrahydrofuran, benzene, toluene, methylene chloride, and pyridine |
| Melting Point | 240°C |
| Softening Temperature | Begins to soften at $\approx 85^{\circ}\text{C}$ |
| Flash Point | 345°C to 360°C |
| Auto-ignition Temperature | 427°C |
| Refractive Index | 1.591 |
| Spectroscopy Data | λ_{max} at 260 nm, 215 nm, 194 nm and 80 nm |

Table 3. Properties of Styrene.⁴

| | |
|---------------------------------|--|
| Form | Colorless to yellowish, very refractive oily liquid |
| Density | 0.9059 |
| Solubility | Soluble in alcohol, ether, methanol, acetone, and carbon disulfide; sparingly soluble in water |
| Melting Point | 30.6° |
| Boiling Point | 145° to 146° |
| Flash point (closed cup) | 31°C |
| Refractive Index | 1.5463 |

Table 4. Properties of Styrene/Butadiene Copolymer.⁵

| | |
|-------------------------|-----------------|
| Form | Amorphous solid |
| Density | 0.933 |
| Refractive Index | 1.5345 |
| Melting Point | -59 to -64°C |

Table 5. Properties of 1,3-Butadiene.⁹

| | |
|--------------------------------|---|
| Form | Colorless gas |
| Relative Molecular Mass | 54.09 |
| Solubility | Sparingly soluble in water (1 g/L at 20°C); slightly soluble in ethanol and methanol; soluble in benzene, carbon tetrachloride, and diethyl ether |

Table 6. Composition and Properties of Trade Name Materials

| Ingredient Name and Trade Name | Composition/Impurities | Properties |
|---|---|---|
| Styrene/Acrylates Copolymer (Sunspheres™ LCG Polymer) | styrene/acrylates copolymer (up to 28%), individual residual monomers (< 100 ppm maximum; for styrene, butyl methacrylate, and methyl methacrylate), aqua ammonia (up to 0.1%), water (up to 74%), and mixture of 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1) (up to 23 ppm). Impurity: copper (0.7 ppm). ⁵⁹ | pH: 6.50-7.5. ⁵⁹ |
| Styrene/Acrylates Copolymer (Sunspheres™ Powder) | styrene/acrylates copolymer (up to 90%), individual residual monomers (≤ 100 ppm maximum; for styrene, butyl methacrylate, and methyl methacrylate), fatty acid ethoxylate (up to 11%), related reaction products (up to 2%), and water (up to 3%). Byproducts and impurities: 1,4-dioxane (1.23 ppm), toluene (< 0.05 ppm), 2-methyl-4-isothiazolin-3-one (5 ppm), and diethylene glycol (64 ppm), and iron (2 ppm). ²⁸ | |
| Styrene/Acrylates Copolymer (OPULYN™ 302B Opacifier) | styrene/acrylic copolymers (up to 41%), individual residual monomers (< 500 ppm maximum), styrene (≤ 50 ppm), water (up to 61%), and benzoic acid (up to 0.5%). Impurities: iron (2,153 ppb) and magnesium (1,735 ppb). ³² | molecular weight: > 1,000,000. ³² |
| Styrene/Acrylates Copolymer (ACUDYNE™ Shine Polymer) | styrene/acrylates copolymer (up to 41%), individual residual monomers (< 100 ppm; for styrene, butyl acrylate, and 2-ethyl hexyl acrylate), water (up to 61%), and benzoic acid (up to 0.75%). Impurities: chromium (70 ppb), iron (333-1996 ppb), and nickel (92 ppb). ²⁹ | pH: 3-5. ²⁹ |
| Styrene/Acrylates Copolymer (SunSpheres™ PGL Polymer) | styrene/acrylates copolymer (up to 26%), residual monomers (< 100 ppm; for styrene, butyl methacrylate, and methyl methacrylate), aqua ammonia (up to 0.1%), pentylene glycol (up to 6%), and water (up to 69%). Impurity: iron (1 ppm). ⁶⁰ | pH: 6.5-7.5. ⁶⁰ |
| Styrene/Acrylates Copolymer (OPULYN™ 301 Opacifier) | styrene/acrylic copolymer (up to 41%), water (up to 61%), residual monomers (< 500 ppm), and styrene (≤ 20 ppm). Impurities: heavy metals not detected. ⁵⁰ | molecular weight: > 1,000,000; pH: 2.05-2.50. ⁵⁰ |
| Styrene/Acrylates Copolymer (ACUDYNE™ Bold Polymer) | styrene/acrylates copolymer (up to 41%), individual residual monomers (< 100 ppm; for styrene, butyl acrylate, 2-ethyl hexyl acrylate), water (up to 61%), and benzoic acid (up to 0.75%). Impurities: chromium (82 ppb), iron (2,270 ppb), and nickel (173 ppb). ³⁰ | pH: 3-5. ³⁰ |
| Styrene/Acrylates Copolymer (Syntran® 5903; corresponds to CAS Nos. 9011-14-7 and 9010-92-8) | dry extract of 35% styrene/acrylates copolymer + 65% water. ³³ | white, milky dispersion (pH 7). ³³ |
| Styrene/Acrylates Copolymer (Syntran® 5904; (corresponds to CAS Nos. 9011-14-7 and 9010-92-8) | dry extract of 40% styrene/acrylates copolymer + 60% water. ³⁵ | white, milky dispersion (pH 2.5). ³⁵ |
| Styrene/Acrylates Copolymer (Syntran® 5905; (corresponds to CAS Nos. 9011-14-7 and 9010-92-8) | dry extract of 40% styrene/acrylates copolymer + 60% water. ³⁶ | white, milky dispersion (pH 2.5). ³⁶ |
| Styrene/Acrylates Copolymer (Syntran® 5907; (corresponds to CAS Nos. 9003-63-8 and 9010-92-8) | dry extract of 40% styrene/acrylates copolymer + 60% water. ³⁴ | white, milky dispersion (pH 2.5). ³⁴ |

Table 6. Composition and Properties of Trade Name Materials

| Ingredient Name and Trade Name | Composition/Impurities | Properties |
|--|---|--|
| Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer | Both are used in ingredient mixtures in which the total polymer content is usually in the range of 5 to 20 weight % and the main component may be either of the following: mineral oil, isohexadecane, isododecane, hydrogenated polyisobutene, isopropyl palmitate, isononyl isononanoate, and residual monomer (below limit of detection [100 ppb]) ¹¹ | |
| Polyacrylate-15 (Syntran® PC 5208; corresponds to CAS No. 67892-91-5) | contains the following: olefin-acrylic graft polymer (37%), ethoxylated secondary alcohol (3%), 1,3-butanediol (2%), 0.20% methylparaben, 0.15% propylparaben, residual monomer (< 5 ppm), and water (58%). ⁴⁴ | molecular weight reported as $m + n > 100$. ⁴⁴ |
| Polyacrylate-18 and Polyacrylate-19 (Syntran® PC 5117; corresponds to CAS No. 848236-12-4) | contains the following: acrylate copolymer (35%), 1,3-butanediol (4%), methylparaben (0.20%), propylparaben (0.15%), residual monomer (< 5 ppm), and water (60%). ⁴⁵ | molecular weight reported as $n > 50$. ⁴⁵ |
| Polyacrylate-18 and Polyacrylate-19 (Syntran® PC 5107; corresponds to CAS No. 848236-12-4) | contains the following: acrylate copolymer (30%), 1,3-butanediol (4%), methylparaben (0.20%), propylparaben (0.15%), residual monomer (< 5 ppm), and water (65%). ⁴⁶ | molecular weight reported as $n > 50$. ⁴⁶ |
| Polyacrylate-21 (Syntran® PC 5100 CG (corresponds to CAS Nos. 68541-61-7 and 26316-50-7) | acrylate copolymers in an aqueous phase. dry extract of 25% non-volatiles. ⁴⁷ | typical pH: 8.0. ⁴⁷ |
| Polystyrene (Syntran® 5900) | contains the following: polystyrene (31% to 33%), surfactants (2% to 3%), residual monomer (< 5 ppm), and balance is water. ⁴² | molecular weight of ~ 50,000 daltons. ⁴² |

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.^{12,13}

| | Ethylene/Propylene/Styrene Copolymer | | Butylene/Ethylene/Styrene Copolymer | | Butyl Acrylate/Styrene Copolymer | |
|---------------------------------------|---|-----------|--|-------------|---|-----------|
| | # of Uses | Conc. (%) | # of Uses | Conc. (%) | # of Uses | Conc. (%) |
| Totals/Conc. Range | 413 | 0.075-8.2 | 400 | 0.008-8.2 | NR | 0.25 |
| Duration of Use | | | | | | |
| <i>Leave-On</i> | 408 | 0.075-8.2 | 395 | 0.008-8.2 | NR | NR |
| <i>Rinse off</i> | 5 | 0.18 | 5 | 0.11-0.95 | NR | 0.25 |
| <i>Diluted for (bath) Use</i> | NR | NR | NR | 0.95 | NR | NR |
| Exposure Type | | | | | | |
| <i>Eye Area</i> | 16 | 0.075-2.3 | 19 | 0.01-0.25 | NR | NR |
| <i>Incidental Ingestion</i> | 324 | 6-8.2 | 314 | 1-8.2 | NR | NR |
| <i>Incidental Inhalation- Sprays</i> | 32 | 0.5 | 29 | 1.9** | NR | NR |
| <i>Incidental Inhalation- Powders</i> | 27 | 0.5 -3.9* | 25 | 0.008-0.84* | NR | NR |
| <i>Dermal Contact</i> | 72 | 0.075-3.9 | 70 | 0.008-1.9 | NR | NR |
| <i>Deodorant (underarm)</i> | NR | NR | NR | NR | NR | NR |
| <i>Hair - Non-Coloring</i> | 3 | 1-2 | 2 | NR | NR | 0.25 |
| <i>Hair-Coloring</i> | NR | NR | NR | NR | NR | NR |
| <i>Nail</i> | 2 | 3-5.7 | 2 | 0.18-1.9 | NR | NR |
| <i>Mucous Membrane</i> | 328 | 6-8.2 | 318 | 0.11-8.2 | NR | NR |
| <i>Baby Products</i> | NR | NR | NR | NR | NR | NR |
| | Hydrogenated Butylene/Ethylene/Styrene Copolymer | | Hydrogenated Ethylene/Propylene/Styrene Copolymer | | Hydrogenated Styrene/Butadiene Copolymer | |
| | # of Uses | Conc. (%) | # of Uses | Conc. (%) | # of Uses | Conc. (%) |
| Totals/Conc. Range | 22 | 10 | 23 | 1.5-4.4 | 13 | 0.33-18.7 |
| Duration of Use | | | | | | |
| <i>Leave-On</i> | 19 | NR | 20 | 1.5-4.4 | 13 | 0.33-18.7 |
| <i>Rinse off</i> | 3 | 10 | 3 | NR | NR | 2 |
| <i>Diluted for (bath) Use</i> | NR | NR | NR | NR | NR | NR |
| Exposure Type | | | | | | |
| <i>Eye Area</i> | NR | NR | 1 | 2 | NR | 2.3 |
| <i>Incidental Ingestion</i> | 7 | NR | 7 | NR | 8 | 0.33-18.7 |
| <i>Incidental Inhalation- Sprays</i> | 4** | NR | 4** | NR | 2** | NR |
| <i>Incidental Inhalation- Powders</i> | 4* | NR | 4* | NR | 1 | 4* |
| <i>Dermal Contact</i> | 7 | 10 | 8 | 1.5-4.4 | 2 | 2.3-4 |
| <i>Deodorant (underarm)</i> | NR | NR | NR | NR | NR | NR |
| <i>Hair - Non-Coloring</i> | 8 | NR | 8 | NR | 3 | 2 |
| <i>Hair-Coloring</i> | NR | NR | NR | NR | NR | NR |
| <i>Nail</i> | NR | NR | NR | NR | NR | NR |
| <i>Mucous Membrane</i> | 7 | NR | 7 | NR | 8 | 0.33-18.7 |
| <i>Baby Products</i> | NR | NR | NR | NR | NR | NR |
| | Hydrogenated Styrene/Isoprene Copolymer | | Isobutylene/Styrene Copolymer | | Methylstyrene/Vinyltoluene Copolymer | |
| | # of Uses | Conc. (%) | # of Uses | Conc. (%) | # of Uses | Conc. (%) |
| Totals/Conc. Range | 78 | 0.89-4.2 | 1 | 1 | 2 | 0.58 |
| Duration of Use | | | | | | |
| <i>Leave-On</i> | 78 | 0.89-4 | 1 | 1 | 2 | 0.58 |
| <i>Rinse off</i> | NR | 4.2 | NR | NR | NR | NR |
| <i>Diluted for (bath) Use</i> | NR | NR | NR | NR | NR | NR |
| Exposure Type | | | | | | |
| <i>Eye Area</i> | 25 | NR | NR | NR | NR | NR |
| <i>Incidental Ingestion</i> | 30 | 2.5-3 | NR | NR | 2 | NR |
| <i>Incidental Inhalation- Sprays</i> | 2 | 4** | NR | NR | NR | NR |
| <i>Incidental Inhalation- Powders</i> | 5 | 3* | 1 | 1 | NR | NR |
| <i>Dermal Contact</i> | 45 | 0.89-4 | 1 | 1 | NR | 0.58 |
| <i>Deodorant (underarm)</i> | NR | NR | NR | NR | NR | NR |
| <i>Hair - Non-Coloring</i> | 2 | 4.2 | NR | NR | NR | NR |
| <i>Hair-Coloring</i> | NR | NR | NR | NR | NR | NR |
| <i>Nail</i> | 1 | NR | NR | NR | NR | NR |
| <i>Mucous Membrane</i> | 30 | 2.5-3 | NR | NR | 2 | NR |
| <i>Baby Products</i> | 3 | NR | NR | NR | NR | NR |

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.^{12,13}

| | Polystyrene | | Polystyrene/Hydrogenated Polyisopentene Copolymer | | Sodium Styrene/Acrylates Copolymer | |
|---------------------------------------|-----------------------------|------------|---|------------|------------------------------------|--------------|
| | # of Uses | Conc. (%) | # of Uses | Conc. (%) | # of Uses | Conc. (%) |
| Totals/Conc. Range | 19 | 0.08-36.5 | 16 | 0.0002-1.2 | 25 | 0.49 |
| Duration of Use | | | | | | |
| <i>Leave-On</i> | 16 | 0.08-0.4 | 13 | 0.015-1.2 | 19 | 0.49 |
| <i>Rinse off</i> | 3 | 36.5 | 3 | 0.0002 | 4 | NR |
| <i>Diluted for (bath) Use</i> | NR | NR | NR | NR | 2 | NR |
| Exposure Type | | | | | | |
| <i>Eye Area</i> | 2 | NR | 7 | 0.15-1.2 | NR | NR |
| <i>Incidental Ingestion</i> | NR | NR | NR | 0.05 | NR | NR |
| <i>Incidental Inhalation- Sprays</i> | 5 | 0.4** | 2** | NR | 4** | NR |
| <i>Incidental Inhalation- Powders</i> | 4 | 0.2* | 2** | NR | 4* | NR |
| <i>Dermal Contact</i> | 10 | 0.08-36.5 | 16 | 0.0002-1.2 | 22 | NR |
| <i>Deodorant (underarm)</i> | NR | NR | NR | NR | 13 | NR |
| <i>Hair - Non-Coloring</i> | 9 | 0.4 | NR | NR | 3 | NR |
| <i>Hair-Coloring</i> | NR | NR | NR | NR | NR | NR |
| <i>Nail</i> | NR | NR | NR | NR | NR | 0.49 |
| <i>Mucous Membrane</i> | 2 | NR | NR | 0.05 | 2 | NR |
| <i>Baby Products</i> | NR | NR | NR | NR | NR | NR |
| | Styrene/Acrylates Copolymer | | Styrene/Butadiene Copolymer | | Styrene/VP Copolymer | |
| | # of Uses | Conc. (%) | # of Uses | Conc. (%) | # of Uses | Conc. (%) |
| Totals/Conc. Range | 272 | 0.028-35 | 9 | NR | 82 | 0.000038-1 |
| Duration of Use | | | | | | |
| <i>Leave-On</i> | 121 | 0.028-35 | NR | NR | 30 | 0.000038-0.4 |
| <i>Rinse off</i> | 135 | 0.04-12 | 9 | NR | 52 | 0.021-1 |
| <i>Diluted for (bath) Use</i> | 16 | 0.2-0.4 | NR | NR | NR | NR |
| Exposure Type | | | | | | |
| <i>Eye Area</i> | 11 | 0.36-15 | NR | NR | NR | 0.2-0.4 |
| <i>Incidental Ingestion</i> | 3 | 0.13 | NR | NR | 1 | NR |
| <i>Incidental Inhalation- Sprays</i> | 34 | 0.35-3.5 | NR | NR | 22 | 0.12 |
| <i>Incidental Inhalation- Powders</i> | 21 | 0.028-2.7* | NR | NR | 6 | 0.12-0.2* |
| <i>Dermal Contact</i> | 201 | 0.028-17.7 | 8 | NR | 18 | 0.000038-0.4 |
| <i>Deodorant (underarm)</i> | 2 | 0.4 | NR | NR | NR | NR |
| <i>Hair - Non-Coloring</i> | 8 | 0.2-1 | 1 | NR | 36 | 0.032-1 |
| <i>Hair-Coloring</i> | NR | 0.04-12 | NR | NR | 25 | 0.04-0.7 |
| <i>Nail</i> | 57 | 0.52-35 | NR | NR | 2 | NR |
| <i>Mucous Membrane</i> | 133 | 0.04-7.7 | 8 | NR | 6 | 0.057 |
| <i>Baby Products</i> | 2 | 0.2 | NR | NR | NR | NR |
| | Polyacrylate-5 | | Polyacrylate-15 | | Polyacrylate-16 | |
| | # of Uses | Conc. (%) | # of Uses | Conc. (%) | # of Uses | Conc. (%) |
| Totals/Conc. Range | 3 | NR | 22 | 0.38 | 4 | 1-11.3 |
| Duration of Use | | | | | | |
| <i>Leave-On</i> | 3 | NR | NR | 0.38 | 4 | 1-11.3 |
| <i>Rinse off</i> | NR | NR | 22 | NR | NR | NR |
| <i>Diluted for (bath) Use</i> | NR | NR | NR | NR | NR | NR |
| Exposure Type | | | | | | |
| <i>Eye Area</i> | NR | NR | NR | NR | 4 | 1-4.5 |
| <i>Incidental Ingestion</i> | 2 | NR | NR | NR | NR | 11.3 |
| <i>Incidental Inhalation- Sprays</i> | NR | NR | NR | NR | NR | NR |
| <i>Incidental Inhalation- Powders</i> | NR | NR | NR | 0.38* | NR | NR |
| <i>Dermal Contact</i> | NR | NR | NR | 0.38 | 4 | 1-4.5 |
| <i>Deodorant (underarm)</i> | NR | NR | NR | NR | NR | NR |
| <i>Hair - Non-Coloring</i> | NR | NR | NR | NR | NR | NR |
| <i>Hair-Coloring</i> | NR | NR | 22 | NR | NR | NR |
| <i>Nail</i> | 1 | NR | NR | NR | NR | NR |
| <i>Mucous Membrane</i> | 2 | NR | NR | NR | NR | 11.3 |
| <i>Baby Products</i> | NR | NR | NR | NR | NR | NR |

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.^{12,13}

| | Polyacrylate-21 | |
|---------------------------------------|------------------------|-----------|
| | # of Uses | Conc. (%) |
| Totals*/Conc. Range | NR | 0.7-0.9 |
| Duration of Use | | |
| <i>Leave-On</i> | NR | 0.7-0.9 |
| <i>Rinse off</i> | NR | NR |
| <i>Diluted for (bath) Use</i> | NR | NR |
| Exposure Type | | |
| <i>Eye Area</i> | NR | 0.9 |
| <i>Incidental Ingestion</i> | NR | NR |
| <i>Incidental Inhalation-Sprays</i> | NR | NR |
| <i>Incidental Inhalation -Powders</i> | NR | 0.7 |
| <i>Dermal Contact</i> | NR | 0.7-0.9 |
| <i>Deodorant (underarm)</i> | NR | NR |
| <i>Hair - Non-Coloring</i> | NR | NR |
| <i>Hair-Coloring</i> | NR | NR |
| <i>Nail</i> | NR | NR |
| <i>Mucous Membrane</i> | NR | NR |
| <i>Baby Products</i> | NR | NR |

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

*It is possible that these products may be powders, but it is not specified whether the reported uses are powders.

**It is possible that this product may be a spray, but it is not specified whether the reported use is a spray.

***Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 8. Carcinogenicity Studies/Reviews of Carcinogenic Potential on Copolymers/Monomers

| Copolymer/Monomer | Test Protocol/Basis for Conclusion | Results/Conclusion |
|--------------------------|--|--|
| Polystyrene | Groups of Wistar rats. Subcutaneous implantation of various forms of polystyrene: smooth discs (47 rats); perforated discs (51 rats); rods, spheres, and fibers (40 rats); and powder (number of rats not stated). | Sarcoma incidences: 37 of 47 rats (78.7%), 25 of 51 rats (49%), and 15 of 40 rats (37.5%). Powder did not induce sarcomas. ^{5,61} |
| Polystyrene | Wistar rats (from 3 different laboratory sources; number not stated). | Differences in incidence of local sarcomas (8% to 40%) found, depending on the animal strain. ^{5,62} |
| Styrene | Groups of Fischer 344 rats and B6C3F ₁ mice (50 males, 50 females/species) in NTP oral carcinogenicity bioassay. Styrene (in corn oil, by gavage) 5 days per week at doses up to 2,000 mg/kg/day (rats) and 300 mg/kg/day (mice). Dosing for 78 weeks (rats: 1,000 and 2,000 mg/kg/day dose groups; mice: 150 and 300 mg/kg/day dose groups) and 103 weeks (rats: 500 mg/kg/day dose group) | No convincing evidence for carcinogenicity of styrene found in rats or mice of either sex. ⁶³ |
| 1,3-Butadiene | Groups of 50 male and 50 female B6C3F ₁ mice in NTP inhalation carcinogenicity study. Exposure to air containing 625 ppm or 1,250 ppm 1,3-butadiene 5 days per week (6 h/day) for 60 or 61 weeks. | Clear evidence of carcinogenicity in male and female mice. ²⁶ |
| 1,3-Butadiene | Groups of 70 male and 70 female B6C3F ₁ mice in NTP inhalation carcinogenicity study. Exposure to air containing 6.25, 20, 62.5, or 200 ppm 1,3-butadiene 5 days/week (6 h/day) for up to 2 years | Clear evidence of carcinogenicity in male and female mice. ⁶⁴ |
| 1,3-Butadiene | Groups of 90 male and 90 female B6C3F ₁ mice in NTP inhalation carcinogenicity study. Exposure to 625 ppm 1,3-butadiene 5 days/week (6 h/day) for up to 2 years | Clear evidence of carcinogenicity in male and female mice. ⁶⁴ |
| Styrene | Sufficient evidence of carcinogenicity from studies involving experimental animals. Limited evidence of carcinogenicity of styrene in humans based on studies of workers exposed to styrene that showed: (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers | According to the NTP, styrene reasonably anticipated to be a human carcinogen. ⁶⁵ |
| Styrene | Limited evidence of carcinogenicity of styrene in humans and in experimental animals | According to IARC, styrene possibly carcinogenic to humans. ²² |
| Styrene | | According to the the United States EPA, styrene possibly carcinogenic to humans. ⁶⁶ |
| 1,3-Butadiene | Unit cancer risk estimate of 0.08/ppm, based on linear modeling and extrapolation of human data | According to the United States EPA, 1,3-butadiene carcinogenic to humans by inhalation exposure. ⁶⁷ |
| 1,3-Butadiene | 1,3-Butadiene causes cancer of the hematolymphatic organs. There is strong evidence that carcinogenicity of 1,3-butadiene in humans operates by a genotoxic mechanism that involves formation of reactive epoxides, the interaction of these direct-acting mutagenic epoxides with DNA, and resultant mutagenicity. | According to IARC, sufficient evidence for carcinogenicity of 1,3-butadiene in humans and in experimental animals. ⁶⁸ |

Table 8. Carcinogenicity Studies/Reviews of Carcinogenic Potential on Copolymers/Monomers

| Copolymer/Monomer | Test Protocol/Basis for Conclusion | Results/Conclusion |
|-----------------------------|--|---|
| Styrene/Butadiene Copolymer | Multi-plant cohort studies of male styrene/butadiene rubber workers | Significantly increased cancer risks, including risks of non-Hodgkin's lymphoma (NHL), NHL-chronic lymphocytic leukemia, and leukemia. ^{69,70} |
| Styrene/Butadiene Copolymer | Epidemiological information on styrene/butadiene copolymer workers | According to IARC, this epidemiological information suggests elevated risk for lymphato-hematopoietic malignancies. ⁵ |
| Polyacrylate | Cross-sectional respiratory survey of 164 workers exposed to polyacrylate dust for average of 20.7 years | No evidence of excess risk of lung cancer. ⁷¹ |

References

1. Britovsek, G. J. P. Gibson V. C. and Wass D. F. The search for new-generation olefin polymerization catalysts: Life beyond metallocenes. *Angew.Chem.Int.Ed.* 1999;38:428-447.
2. Nikitakis, J. and Breslawec H. P. International Cosmetic Ingredient Dictionary and Handbook. 14 *ed.* Washington, DC: Personal Care Products Council, 2014.
3. International Programme on Chemical Safety (IPCS).2012.
Polystyrene. <http://www.inchem.org/documents/icsc/icsc/eics1043.htm>. Date Accessed 2-5-2014.
4. O'Neil, M. J. Heckelman P. E. Dobbelaar P. H. Roman K. J. and Kenny C. M. The Merck Index: an encyclopedia of chemicals, drugs, and biologicals. 15th *ed.* Cambridge, UK: Royal Society of Chemistry, 2013.
5. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Some monomers, plastics and synthetic elastomers, and acrolein. Volume 19. <http://www.iarc.fr>. Date Accessed 2-7-2014.
6. Zitting, A. and Heinonen, T. Decrease of reduced glutathione in isolated rat hepatocytes caused by acrolein, acrylonitrile and the thermal degradation products of styrene copolymers. *Toxicology*. 1980;17(3):1981-342.
7. Zitting, A. Thermal degradation products of polyethylene, polypropylene, polystyrene, polyvinylchloride, and polytetrafluoroethylene in the processing of plastics. <http://www.niwl.se/ah/ah.htm>.
8. Bond, J. A. Review of the toxicology of styrene. *Critical Reviews in Toxicology*. 1989;19(3):227-249.
9. International Agency for Research on Cancer (IARC). IARC Monograph Volume 100F. 1,3-Butadiene. 2009. <http://monographs.iarc.fr/ENG/monographs/vol100F/mono100F-26.pdf>. Date Accessed 2-7-2014.
10. ANONYMOUS. Polystyrene - half a century of development and innovation. *Plast.Rubber Int.* 1981;6(4):158.
11. Personal Care Products Council. Information on ethylene/propylene/styrene copolymer and butylene/ethylene/styrene copolymer. Unpublished data submitted by the Personal Care Products Council on 4-24-2014. 2014. pp.1
12. Food and Drug Administration (FDA). Information supplied to FDA by industry as part of the VCRP FDA database. 2013. Washington, D.C.: FDA.
13. Personal Care Products Council. Concentration of use by FDA product category. Styrene and vinyl-type styrene copolymers. Unpublished data submitted by the Personal Care Products Council on 2-4-2014. 2014.
14. Rothe H. Special aspects of cosmetic spray evaluation. 2011.
15. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. <http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf>. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.
16. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;24-27.
17. Ahmad, M. and Bajahlan A. S. Leaching of styrene and other aromatic compounds in drinking water from PS bottles. *Journal of Environmental Sciences*. 2007;19:421-426.
18. Nakagami, G. Sanada H. Konya C. Kitagawa A. Tadaka E. and Tabata K. Comparison of two pressure ulcer preventive dressings for reducing shear force on the heel. *J.Wound Ostomy Continence Nurs.* 2006;33:267-272.

19. Food and Drug Administration (FDA). Polystyrene and rubber-modified polystyrene. 21CFR 177.1640. 2013.
20. Food and Drug Administration (FDA). Synthetic flavoring substances and adjuvants. Styrene. 21CFR 172.515. 2013.
21. Food and Drug Administration (FDA). Everything added to food in the United States (EAFUS). 21CFR: 172.615, 175.105, 175.125, 175.300, 176.170, 176.180, 177.1010, 177.1200, 177.2600, 177.2800, 178.1005, 178.3790, and 181.30. 2014.
22. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. Volume 82. <http://www.iarc.fr>. Date Accessed 2-7-2014.
23. Berode, M. Droz P. and Guillemin M. Human exposure to styrene VI. Percutaneous absorption in human volunteers. *Int.Arch.Occup.Environ.Health*. 1985;55:331-336.
24. Maestri, L. Imbriani M. Ghittori S. Capodaglio E. Gobba F. and Cavalleri A. Excretion of N-acetyl-S-(1-phenyl-2-hydroxyethyl)-cysteine and N-acetyl-S-(2-phenyl-2-hydroxyethyl)-cysteine in workers exposed to styrene. *Sci.total Environ*. 1997;199(1-2):13-22.
25. Brugnone, F. Perbellini L. Wang G. Z. Maranelli G. Raineri E. De Rosa E. Saletti C. Soave C. and Romeo L. Blood styrene concentrations in a "normal" population and in exposed workers 16 hours after the end of the workshift. *Int.Arch.Occup.Environ.Health*. 1993;65(2):125-130.
26. National Toxicology Program (NTP). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F₁ mice (inhalation studies). National Toxicology Program Technical Report Series No. 288. <http://ntp.niehs.nih.gov>. Date Accessed 2-7-2014.
27. Shugaev, B. B. and Yaroslavl B. S. Concentrations of hydrocarbons in tissues as a measure of toxicity. *Arch.Environ.Health*. 1969;18:878-882.
28. The Dow Chemical Company. SunsphearsTM Powder (86-90% styrene/acrylates copolymer) global cosmetic dossier. Unpublished data submitted by the Personal Care Products Council on 4-10-2014. 2013. pp.1-12.
29. The Dow Chemical Company. AcudyneTM SHINE Polymer (39-41% styrene/acrylates copolymer) global cosmetic dossier. Unpublished data submitted by the Personal Care Products Council on 4-10-2014. 2012. pp.1-13.
30. The Dow Chemical Company. AcudyneTM Bold Polymer (39-41% styrene/acrylates copolymer) global cosmetic dossier. Unpublished data submitted by the Personal Care Products Council on 4-10-2014. 2012. pp.1-13.
31. Stillmeadow. Acute oral toxicity study. Trade name mixture containing 4-15% ethylene/propylene/styrene copolymer and 0.1-2.0% butylene/ethylene/styrene copolymer. Unpublished data submitted by the Personal Care Products Council on 4-24-2014. 1994. pp.1
32. The Dow Chemical Company. OpulynTM 302B Opacifier (39-41% styrene/acrylates copolymer) global cosmetic dossier. Submission of unpublished data by the Personal Care Products Council on 4-10-2014. 2013. pp.1-11.
33. Evic France. Toxicological assessment report Syntran 5903 (styrene acrylates copolymer). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2005. pp.1-2.
34. Evic France. Toxicological assessment certificate referring to a complex ingredient intended to be used in cosmetic products. Syntran 5907 (styrene acrylates copolymer). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2009. pp.1-3.
35. Evic France. Toxicological assessment report on Syntran 5904 (styrene acrylates copolymer). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2005. pp.1-2.

36. Evic France. Toxicological assessment report on Syntran 5905 (styrene acrylates copolymer). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2005. pp.1-2.
37. The Procter & Gamble Co. Letter to USEPA concerning the status of the chronic inhalation study being conducted at Lovelace Inhalation Toxicology Research Inst. on polyacrylate polymer with attachments. NTIS Report No. OTS00004703*DL. 1990. pp.1-11.
38. Institute for Polyacrylate Absorbents. Initial submission: Letter submitting a status update for a chronic inhalation study in rats on polyacrylate polymer. NTIS Report No. OTS0534892*DL. 1991. pp.1-3.
39. United States Environmental Protection Agency (EPA). Integrated Risk Information System (IRIS). Reference dose for chronic oral exposure (RfD) to styrene. 1990. <http://www.epa.gov/iris/subst/0104.htm>. Date Accessed 2-7-2014.
40. Quast, J. F. Humiston C. G. Kalnins R. Y. et. al. Results of a toxicity study of monomeric styrene administered to beagle dogs by oral intubation for 19 months. In: Environmental Protection Agency's Integrated Risk Information System (IRIS). <http://www.epa.gov/iris/subst/0104.htm>. Date Accessed 2-7-2014.
41. Stillmeadow. Primary eye irritation study. Trade name mixture containing 4-15% ethylene/propylene/styrene copolymer and 0.1-2.0% butylene/ethylene/styrene copolymer. Unpublished data submitted by the Personal Care Products Council on 4-24-2014. 1992.
42. Toxicology Regulatory Services. Interpolymer cosmetic ingredient safety dossier. Syntran 5900 (polystyrene). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2013.
43. Carpenter, C. Shaffer C. Weil C. and Smyth H. Studies on the inhalation of 1,3-butadiene; with a comparison of its narcotic effect with benzol, toluol, and styrene, and a note on the elimination of styrene by the human. *J.Ind.Hyg.Tox.* 1944;26:69-78.
44. Toxicology Regulatory Services. Interpolymer cosmetic ingredient safety dossier. Syntran PC 5208 (polyacrylate-15). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2014. pp.1-2.
45. Toxicology Regulatory Services. Interpolymer cosmetic ingredient safety dossier on Syntran PC 5117 (polyacrylate-18 and polyacrylate-19). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2014.
46. Toxicology Regulatory Services. Interpolymer cosmetic ingredient safety dossier on Syntran PC 5107 (polyacrylate-18 and polyacrylate-19). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2014. pp.1-3.
47. Interpolymer. Cosmetic ingredient safety dossier on Syntran PC 5100CG (polyacrylate-21 and dimethylaminoethyl methacrylate copolymer). Unpublished data submitted by the Personal Care Products Council on 4-21-2014. 2014. pp.1-3.
48. Stillmeadow. Primary dermal irritation study in rabbits. Trade name mixture containing 4-15% ethylene/propylene/styrene copolymer and 0.1-2.0% butylene/ethylene/styrene copolymer. Unpublished data submitted by the Personal Care Products Council on 4-24-2014. 1992. pp.1
49. Sjöborg, S. Dahlquist I. Fregert S. and Trulsson L. Contact allergy to styrene with cross reaction to vinyltoluene. *Contact Dermatitis.* 1982;8(3):207-208.
50. The Dow Chemical Company. Opulyn™ 301 Opacifier (39-41% styrene/acrylates copolymer) global cosmetic dossier. Unpublished data submitted by the Personal Care Products Council on 4-10-2014. 2012. pp.1-12.
51. Stephens & Associates. Human repeat insult patch test. Trade name mixture containing 4-15% ethylene/propylene/styrene copolymer and 0.1-2.0% butylene/ethylene/styrene copolymer. Unpublished data submitted by the Personal Care Products Council on 4-24-2014. 1994. pp.1

52. Sjöborg, S. Fregert S. and Trulsson L. Contact allergy to styrene and related chemicals. *Contact Derm.* 1984;10:94-96.
53. National Toxicology Program (NTP). NTP-CERHR monograph on the potential human reproductive and developmental effects of styrene. NIH Publication No. 06-4475. <http://ntp.niehs.nih.gov>.
54. National Toxicology Program (NTP). Polystyrene. Genetic toxicology - bacterial mutagenicity. Study AD: A14107. <http://tools.niehs.nih.gov/cebs3/ntpViews/?studyNumber=A14107>. Date Accessed 2-6-2014.
55. National Research Council. Review of the styrene assessment in the National Toxicology Program 12th Report on Carcinogens (2014). Washington, D.C.
56. National Toxicology Program (NTP). Substances nominated to the report on carcinogens. Polyacrylates. <http://ntp.niehs.nih.gov/go/37893>. Date Accessed 7-30-2014.
57. TNO Nutrition & Food Research Institute. Determination of estrogenic activity in F2L5250 (low molecular weight polystyrene) in the Tiecco test with rats, with cover letter dated 7/24/96. NTIS Report No. OTS058474-1. 1996. pp.1-27. Alexandria: National Technical Information Service.
58. International Programme on Chemical Safety (IPCS). Polystyrene. <http://www.inchem.org/documents/icsc/icsc/eics1043.htm>. Date Accessed 2-5-2014.
59. The Dow Chemical Company. SunSpheres™ LCG Polymer (26-28% styrene/acrylates copolymer) global cosmetic dossier. Unpublished data submitted by the Personal Care Products council on 4-10-2014. 2013. pp.1-12.
60. The Dow Chemical Company. SunSpheres™ PGL Polymer (25-26% styrene/acrylates copolymer) global cosmetic dossier. Unpublished data submitted by the Personal Care Products Council on 4-10-2014. 2013. pp.1-11.
61. Nothdurft, H. Experimental formation of sarcomas due to foreign bodies (German). *Strahlentherapie.* 1956;100:192-210.
62. Rivière, M. R. Chouroulinkow I. and Guérin M. Sarcomas produced by implantation of polystyrene in rats: results appreciably different according to the strain of animals used (French). *C.R.Soc.Biol.* 1960;154:485-487.
63. National Cancer Institute. Bioassay of styrene for possible carcinogenicity. CAS No. 100-42-5. NCI-CG-TR-185. Technical Report Series No. 185. Bethesda: National Cancer Institute, 1979.
64. National Toxicology Program (NTP). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F₁ mice (inhalation studies). Technical Report No. 434. Date Accessed 4-28-2014.
65. National Toxicology Program (NTP). Report on Carcinogens. Twelfth Edition. <http://ntp.niehs.gov/ntp/roc/twelfth/roc12.pdf>. Date Accessed 2-6-2014.
66. United States Environmental Protection Agency (EPA). Styrene. <http://www.wpa.gov/ttnatw/hlthef/styrene.html>. Date Accessed 2-7-2014.
67. United States Environmental Protection Agency (EPA). Health assessment of 1,3-butadiene. National Center for Environmental Assessment, Washington, DC. EPA/600/P-98/001F. 2002. <http://www.epa.gov/ncea>. Date Accessed 2-7-2014.
68. International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, vol. 71. Lyon, France: IARC, 1999.
69. Graff, J. J. Sathiakumar N. Macaluso M. Maldonado G. Matthews R. and Delzell E. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. *J.Occup.Environ.Med.* 2005;47(9):916-932.

70. Delzell, E. Sathiakumar N. Graff J. Macaluso M. Maldonado G. and Matthews R. An updated study of mortality among North American synthetic rubber industry workers. *Res.Rep.Health Eff.Inst.* 2006;132:1-74.
71. BF Goodrich Co. Initial submission: Final report. Occupational health survey of the respiratory status of polyacrylate workers, with cover letter dated 6/3/96. NTIS Report No. OTS0558536.