TOXICOLOGICAL PROFILE FOR STYRENE

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

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Styrene, Draft for Public Comment was released in October 2007. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
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FOREWORD

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

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

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

Each profile includes the following:

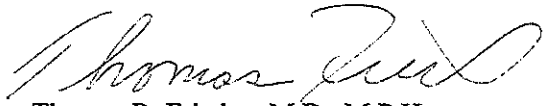
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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



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*Legislative Background

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

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

Other Sections of Interest:

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

ATSDR Information Center

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

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

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

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

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

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

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

Referrals

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

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

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

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

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PEER REVIEW

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

Draft for Public Comment:

1. George Cruzan, Ph.D., DABT, ToxWorks, Bridgeton, New Jersey;

2. Teresa Leavens, Ph.D., Research Assistant Professor, Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University, Raleigh, North Carolina; and

3. Jean Rabovsky, Ph.D., Retired Toxicologist, El Cerrito, California.

These experts collectively have knowledge of styrene'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 styrene 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. Styrene has been found in at least 251 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which styrene 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 styrene, 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 STYRENE?

Description	Styrene is a colorless liquid that evaporates easily. In its pure form, styrene has a sweet smell. Manufactured styrene may contain aldehydes, which give it a sharp, unpleasant odor.

Uses **• Manufacturing**	Large amounts of styrene are produced in the United States. Small amounts are produced naturally by plants, bacteria, and fungi. Styrene is also present in combustion products such as cigarette smoke and automobile exhaust.
• Consumer products	Styrene is widely used to make plastics and rubber. Consumer products containing styrene include: • packaging materials • insulation for electrical uses (i.e., wiring and appliances) • insulation for homes and other buildings • fiberglass, plastic pipes, automobile parts • drinking cups and other "food-use" items • carpet backing These products mainly contain styrene linked together in long chains (polystyrene). However, most of these products also contain a small amount of unlinked styrene.

For more information on the physical and chemical properties of styrene, and its production, disposal, and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO STYRENE WHEN IT ENTERS THE ENVIRONMENT?

Sources	Styrene can be found in air, soil, and water after release from the manufacture, use, and disposal of styrene-based products.
Break down **• Air**	Styrene is quickly broken down in the air, usually within 1–2 days.
• Water and soil	Styrene evaporates from shallow soils and surface water. Styrene that remains in soil or water may be broken down by bacteria or other microorganisms.

For more information on styrene in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO STYRENE?

Air	The primary way you can be exposed to styrene is by breathing air containing it. Releases of styrene into the air occur from: • industries using or manufacturing styrene • automobile exhaust • cigarette smoke, and • use of photocopiers Rural or suburban air generally contains lower concentrations of styrene than urban air. Indoor air often contains higher levels of styrene than outdoor air. • 0.06–4.6 parts per billion (ppb) in outdoor air • 0.07–11.5 ppb in indoor air
Water and soil	Styrene is occasionally detected in groundwater, drinking water, or soil samples. Drinking water containing styrene or bathing in water containing styrene may expose you to low levels of this chemical.
Workplace air	A large number of workers are potentially exposed to styrene. The highest potential exposure occurs in the reinforced-plastics industry, where workers may be exposed to high air concentrations and also have dermal exposure to liquid styrene or resins. Workers involved in styrene polymerization, rubber manufacturing, and styrene-polyester resin facilities and workers at photocopy centers may also be exposed to styrene.
Food	Low levels of styrene occur naturally in a variety of foods, such as fruits, vegetables, nuts, beverages, and meats. Small amounts of styrene can be transferred to food from styrene-based packaging material.

For more information on human exposure to styrene, see Chapter 6.

1.4 HOW CAN STYRENE ENTER AND LEAVE MY BODY?

Enter your body	
• **Inhalation**	When you breathe air containing styrene, most of the styrene will rapidly enter your body through your lungs.
• **Ingestion**	Styrene in food or water may also rapidly enter your body through the digestive tract.
• **Dermal contact**	A very small amount may enter through your skin when you come into contact with liquids containing styrene.
Leave your body	Once in your body, styrene is broken down into other chemicals. Most of these other chemicals leave your body in the urine within few days.

For more information on how styrene enters and leaves the body, see Chapter 3.

1.5 HOW CAN STYRENE AFFECT MY HEALTH?

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

Health Effects	
Workers	
• **Inhalation**	The most common health problems in workers exposed to styrene involve the nervous system. These health effects include changes in color vision, tiredness, feeling drunk, slowed reaction time, concentration problems, and balance problems. The styrene concentrations that cause these effects are more than 1,000 times higher than the levels normally found in the environment.
Laboratory animals	
• **Inhalation**	Hearing loss has been observed in animals exposed to very high concentrations of styrene. Animal studies have shown that inhalation of styrene can result in changes in the lining of the nose and damage to the liver; however, animals may be more sensitive than humans to the nose and liver effects.

Laboratory animals **• Oral**	Impaired learning has been observed in rats exposed to high doses of styrene. Sperm damage has also been observed in rats exposed to high doses of styrene.
Cancer	The International Agency for Research on Cancer has determined that styrene is a possible carcinogen.

Further information on the health effects of styrene in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN STYRENE AFFECT CHILDREN?

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

Effects in children	There are no studies evaluating the effect of styrene exposure on children or immature animals. It is likely that children would have the same health effects as adults. We do not know whether children would be more sensitive than adults to the effects of styrene.
Birth defects	Studies in workers have examined whether styrene can cause birth defects or low birth weight; however, the results are inconclusive. No birth defects were observed in animal studies.
Breast milk	Nursing infants can be exposed to styrene from breast milk.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO STYRENE?

Tobacco smoke	Styrene is a component of tobacco smoke. Avoid smoking in enclosed spaces like inside the home or car in order to limit exposure to children and other family members.
Copier	Styrene is released during the use of home copiers. Families should use a copier only when needed and turn it off when finished. It is also important to keep the room with the copier well ventilated.

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

Detecting exposure	Styrene can be measured in blood, urine, and body tissues for a short time following exposure to moderate-to-high levels.
Measuring exposure	The presence of styrene breakdown products (metabolites) in urine might indicate that you were exposed to styrene; however, these metabolites can also form when you are exposed to other substances. Measuring styrene metabolites in urine within 1 day of exposure allows medical personnel to estimate actual exposure level. The detection of these metabolites in your urine cannot be used to predict the kind of health effects that might develop from that exposure.

Information about tests for detecting styrene in the body is given in Chapters 3 and 7.

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 styrene include the following:

Drinking water	The EPA has determined that exposure to styrene in drinking water at concentrations of 20 ppm for 1 day or 2 ppm for 10 days is not expected to cause any adverse effects in a child. The EPA has determined that lifetime exposure to 0.1 ppm styrene in drinking water is not expected to cause any adverse effects.
Bottled water	The FDA has determined that the styrene concentration in bottled drinking water should not exceed 0.1 ppm.
Workplace air	OSHA set a legal limit of 100 ppm styrene in air averaged over an 8-hour work day.

For more information on regulations and advisories, see Chapter 8.

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 Environmental Medicine
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

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

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO STYRENE IN THE UNITED STATES

Styrene is a high production chemical; the production capacity for styrene in the United States was over 12 billion pounds in 2008. Small amounts of styrene are naturally present in foods such as legumes, beef, clams, eggs, nectarines, and spices. It can also be present in packaged foods by migration from polystyrene food containers and packaging materials. Styrene is a combustion product of cigarette smoke and automobile exhaust. Manufactured styrene is primarily used in the production of polystyrene plastics and resins used principally for insulation or in the fabrication of fiberglass boats; production of copolymers such as styrene-acrylonitrile and acrylonitrile-butadiene-styrene, which are used to manufacture piping, automotive components, and plastic drinking glasses; production of styrene-butadiene rubber used to manufacture car tires, hoses for industrial purposes, and shoes; or formulated with unsaturated polyester resins used as fiberglass reinforcement materials. Styrene copolymers are also frequently used in liquid toner for photocopiers and printers.

Median styrene concentrations in urban and rural/suburban air samples are 0.07–4.6 ppb and 0.06–0.1 ppb. The median styrene concentration in indoor air samples ranged from 0.07 to 11.5 ppb; the primary sources of styrene in indoor air are cigarette smoke and photocopiers. Styrene is rarely detected in drinking water samples and is rarely detected in soil samples.

General population exposure to styrene in air and food has been estimated to be 18–54 and 0.2–1.2 μg/person/day, respectively, with a total daily exposure of 18.2–55.2 μg/day or 0.0003–0.0008 mg/kg/day (assuming a 70-kg reference body weight).

2.2 SUMMARY OF HEALTH EFFECTS

Styrene-induced neurotoxicity has been reported in workers since the 1970s. Studies over the last 15 years have firmly established the central nervous system as the critical target of toxicity. Both short- and long-term exposures to styrene can result in neurological effects. Acute exposure data are limited to the finding of impaired performance on tests of vestibular function in test subjects exposed to 87–376 ppm for 1–3 hours and studies finding no alterations in performance of neurobehavioral tests (reaction time, color discrimination, and tests of memory or attention) in subjects exposed to 20 or 49 ppm. A variety of neurological effects have been observed in chronically exposed styrene workers;

these effects include decreased color discrimination, vestibular effects, hearing impairment, symptoms of neurotoxicity, particularly ”feeling drunk” and tiredness, delays in reaction time, impaired performance on tests measuring attention and memory, increased vibration perception thresholds, impaired nerve conduction velocity, and EEG alterations. The LOAELs for these effects range from about 10 ppm to 93 ppm. In most of the occupational exposure studies, neurological function tests were conducted in the morning before work, suggesting that the deficits were not acute effects. Results of a meta-analysis suggest that the severity of the some of the neurological symptoms increases with exposure duration. For example, 8, 15, 25, and 35% increases in reaction time were observed in workers exposed to 100 ppm for 2, 4, 6, and 8 work-years, respectively. However, this may also be reflective of higher exposure levels in the past rather than a duration-related increase in severity. The existing data are inadequate to determine whether chronic styrene exposure results in permanent damage. Mixed results have been found in studies examining workers before and after an extended period without styrene exposure. Neurotoxicity studies in animals have primarily focused on effects on hearing and damage to the organ of Corti.

Other effects that have been observed in animal studies include damage to the nasal olfactory epithelium and liver necrosis; testicular damage and developmental effects have also been reported, but the weight of evidence does not support concluding that these are sensitive targets. Damage to the nasal olfactory epithelium was observed in mice after 3 days of exposure. The severity of the lesion progressed from single cell necrosis to atrophy and respiratory metaplasia with increasing exposure duration. The lowest-observed-adverse-effect levels (LOAELs) for these lesions are 80, 50, and 20 ppm for acute, intermediate, and chronic exposure, respectively. Rats do not appear to be as sensitive as mice to the nasal olfactory epithelial damage; an intermediate-duration study identified a no-observed-adverse-effect level (NOAEL) and LOAEL of 500 and 1,000 ppm for focal hyperplasia and a chronic study identified a LOAEL of 50 ppm for atrophy and degeneration. The observed species differences may be due to differences in styrene metabolism in the nasal cavity. In particular, rats have a higher capacity to detoxify styrene oxide with epoxide hydrolases and glutathione S-transferase. Humans are not likely sensitive to the nasal toxicity of styrene because styrene oxide has not been detected and high levels of epoxide hydrolases have been found in *in vitro* assays of human nasal tissue.

Unlike the nasal lesions, the severity of hepatic lesions decreases with increased exposure durations. Severe hepatocellular necrosis was observed in mice exposed to 250 ppm for 3 days; however, continued exposure at this concentration resulted in focal necrosis and an increase in pigmented macrophages. Centrilobular aggregates of siderophages were observed in mice exposed to 200 ppm for 13 weeks; no liver effects were observed at 160 ppm after 2 years of exposure. Rats are less sensitive than mice to liver

toxicity; no liver effects were observed in an intermediate-duration study in which rats were exposed to a styrene concentration 10-fold higher than the concentration eliciting hepatic effects in mice. No alterations in serum markers of liver damage were observed in styrene workers exposed to 40 ppm for approximately 5 years. Liver effects have not been observed in rats orally exposed to 35 mg/kg/day for 105 weeks. Some hepatic alterations (increases in liver weight and small areas of focal necrosis) have been reported in rats exposed to 400 mg/kg for an intermediate duration; however, the studies are poorly reported and lack statistical comparisons with controls. No studies examined systemic end points following acute exposure.

Occupational exposure studies have not found significant increases in the occurrence of stillbirth, infant death, malformations, or low birth weight. An increase in fetal deaths were observed in hamsters exposed to very high concentrations (1,000 ppm on gestation days 6–18) and in rats exposed to 300 ppm on gestation days 6–20. However, most single and multigeneration inhalation and oral exposure animal studies did not find significant alterations in fetus/pup survival, growth, or incidence of abnormalities in rats, mice, rabbits, and hamsters exposed to styrene. Two studies have examined neurodevelopmental effects in rats; one study found some minor effects (slight delays in some developmental landmarks). The other, higher-quality study did not find any significant alterations in a number of neurodevelopmental end points. The National Toxicology Program (NTP) Expert Panel examining the developmental potential of styrene concluded that the human data are not sufficient to evaluate the potential developmental toxicity of styrene in humans and that there was no convincing evidence of developmental toxicity in animals.

Although several epidemiology studies have examined potential reproductive effects in male and female styrene workers, adequate analysis of the data is limited by the lack of exposure information and concomitant exposure to other compounds. Mixed results have been found for increased occurrence of spontaneous abortions and oligomenorrhea. In male workers, sperm abnormalities have been reported (Kolstad et al. 1999a), but not alterations in time-to-pregnancy or fertility rates. No adverse reproductive effects were observed in inhalation and oral multigeneration studies in rats. A series of studies found decreases in spermatozoa counts in rats exposed as adults, as neonates, and through lactation. However, as noted by the NTP Expert Panel, this finding is not consistent with the lack of reproductive effects found in the inhalation two-generation study. The NOAEL identified in the two-generation inhalation study was 500 ppm (6 hours/day), which is roughly equivalent to 230 mg/day using a reference inhalation rate of 0.42 m^3/day. The LOAEL for spermatozoa effects in adult rats was 400 mg/kg (6 days/week), which is roughly equivalent to 158 mg/day using a reference body weight of 0.462 kg.

There are several epidemiologic studies of workers at styrene manufacturing and polymerization facilities and reinforced plastics facilities that suggest an association between occupational exposure and an increased incidence of cancer of the lymphatic and hematopoietic tissues in styrene. However, the reported studies are inconclusive due to exposure to multiple chemicals (including benzene) and the small size of the cohorts. Other studies have reported negative results. More consistent results for increases in the risk of lymphatic and hematopoietic cancers have been observed among workers at styrene-butadiene manufacturing facilities. There is suggestive evidence that these increased risks may be due to exposure to 1,3-butadiene rather styrene exposure; however, it is difficult to separate the risks for styrene and 1,3-butadiene because the exposure is highly correlated. There are no reports of cancer resulting from styrene exposure by the oral or dermal routes in humans. Species differences in styrene carcinogenicity have been detected in animal studies. Inhalation and oral exposure studies in rats have not found significant increases in neoplastic lesions. However, increases in lung tumors have been found in mice following inhalation and oral exposure. The increased production of styrene 7,8-oxide in lung Clara cells and the higher ratio of styrene oxide R- to S-enantiomers likely resulted in the increased sensitivity of mice. Overall, human and animal studies suggest that styrene may be a weak human carcinogen. The International Agency for Research on Cancer (IARC) has assigned styrene to Group 2B, possibly carcinogenic to humans. EPA and DHHS have not evaluated the carcinogenic potential of styrene. One study lists a cancer classification of A4, not classifiable as a human carcinogen based on a 1996 evaluation of the available data.

2.3 MINIMAL RISK LEVELS (MRLs)

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an

example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

Acute-Duration Inhalation MRL

An MRL of 5 ppm has been derived for acute-duration inhalation exposure (14 days or less) to styrene.

The acute-duration inhalation toxicity database for styrene consists of several human experimental studies primarily examining neurotoxicity (Ödkvist et al. 1982; Seeber et al. 2004; Ska et al. 2003; Stewart et al. 1968), systemic toxicity studies in mice (Cruzan et al. 1997, 2001; Morgan et al. 1993a, 1993b, 1993c), neurotoxicity studies in rats (Campo et al. 2001; Crofton et al. 1994; Lataye et al. 2003), mice (Cruzan et al. 1997; DeCeaurriz et al. 1983), and guinea pigs (Lataye et al. 2003), a reproductive toxicity study in mice (Salomaa et al. 1985), and developmental toxicity studies in rats (Murray et al. 1978), mice (Kankaanpää et al. 1980), hamsters (Kankaanpää et al. 1980), and rabbits (Murray et al. 1978). Eye irritation was reported in humans exposed to 99 ppm for 7 hours or 376 ppm for 1 hour (Stewart et al. 1968); nasal irritation was also reported at 376 ppm. A significant inhibition of the vestibular-oculomotor system was observed in subjects exposed to 87 ppm for 1 hour (Ödkvist et al. 1982). Studies by (Stewart et al. 1968) found alterations in tests of balance or coordination in subjects exposed to 376 ppm for 1 hour, but not after exposure to 99 ppm for 7 hours or 216 ppm for 1 hour; the test used in the Stewart et al. (1968) studies is probably less sensitive than those used by Ödkvist et al. (1982). No significant alterations in performance on tests of reaction time were observed in subjects exposed to 20 ppm for 3 hours (Seeber et al. 2004) or 49 ppm for 6 hours with or without four 15-minute peak exposures to 98 ppm) (Ska et al. 2003). Additionally, no significant alterations in color discrimination, olfactory threshold, or performance on neurobehavioral tests of memory or attention were observed in subjects exposed to 49 ppm for 6 hours with or without four 15-minute peak exposures to 98 ppm (Ska et al. 2003).

In mice, the most sensitive target of styrene toxicity appears to be the nasal olfactory epithelium; single cell necrosis was observed following exposure to 80 ppm 6 hours/day for 3 days (Cruzan et al. 2001). At 250 ppm, hepatocellular necrosis and degeneration have been observed (Cruzan et al. 1997; Morgan et al. 1993a, 1993b, 1993c). The severity of this lesion appears to be inversely related to the duration of exposure, with more severe damage observed in mice killed within 3 days of exposure (Morgan et al.

1993a, 1993b, 1993c) compared to animals killed after 2 weeks of exposure (Cruzan et al. 1997; Morgan et al. 1993a). Exposure to 250 ppm 6 hours/day, 5 days/week for 2 weeks also resulted in lethargy and unsteady gait in mice (Cruzan et al. 1997). Impaired performance on a swimming test was observed in mice exposed to 610 ppm for 4 hours, but not in animals exposed to 413 ppm (DeCeaurriz et al. 1983). Exposure of rats to high concentrations (1,000 or 1,600 ppm) 6–8 hours/day for 5–14 days resulted in auditory threshold shifts (indicative of hearing loss) and loss of outer hair cells (OHC) in the organ of Corti (Campo et al. 2001; Crofton et al. 1994; Lataye et al. 2003). No alterations in sperm morphology were observed in mice exposed to 300 ppm styrene 5 hours/day for 5 days (Salomaa et al. 1985) and no developmental effects were observed in rats or rabbits exposed to 600 ppm 7 hours/day on gestational days 6–15 or 6–18, respectively, (Murray et al. 1978) or mice exposed to 250 ppm 6 hours/day on gestational days 6–16 (Kankaanpää et al. 1980). An increase in fetal deaths or resorptions was observed in hamsters exposed to 1,000 ppm 6 hours/day on gestational days 6–18 (Kankaanpää et al. 1980).

These data suggest that the nervous system is the most sensitive target of styrene toxicity in humans following acute-duration inhalation exposure. The lowest LOAEL for a relevant end point in humans is 87 ppm for vestibular impairment in subjects exposed to styrene for 1 hour (Ödkvist et al. 1982). A similar LOAEL (80 ppm) was identified for nasal effects in mice exposed to styrene for 3 days (Cruzan et al. 2001). Although nasal irritation has been observed in humans exposed to 376 ppm for 1 hour (Stewart et al. 1968) and focal hyperplasia in the nasal olfactory epithelium was observed in rats exposed to 1,000 ppm (NOAEL of 500 ppm) for 13 weeks (Cruzan et al. 1997), mice appears to be unusually susceptible to this effect. As discussed in Section 2.2, mice appear to have a greater capacity than humans to generate the reactive metabolite, styrene oxide, in the nasal cavity and a lower capacity to detoxify styrene oxide (Green et al. 2001a). Thus, nasal lesions in mice were not considered suitable as the basis of an MRL. The identification of the nervous system as the critical target of toxicity for styrene is supported by a large number of occupational exposure studies. Delays in reaction time have been observed in workers exposed to 21.9–92 ppm (Cherry et al. 1980; Fallas et al. 1992; Gamberale et al. 1976; Jegaden et al. 1993; Mutti et al. 1984a; Tsai and Chen 1996) and vestibular effects have been observed at 18–36 ppm (Calabrese et al. 1996; Möller et al. 1990; Toppila et al. 2006).

The Ödkvist et al. (1982) study did not identify a NOAEL for vestibular effects; however, a NOAEL of 49 ppm for performance on several tests of reaction time, memory, attention, color discrimination, and olfactory threshold was identified by Ska et al. (2003) in subjects exposed to styrene for 6 hours. Although there is some uncertainty whether deriving an MRL based on a 6-hour exposure study would be

protective of continuous exposure to styrene for 2 weeks, the Ska et al. (2003) study was selected as the basis of an acute duration inhalation MRL for styrene.

In this study (Ska et al. 2003), groups of 24 healthy men (aged 20–50 years) were exposed to 1 ppm (control exposure), 24 ppm, and 24 ppm with four 15-minute exposures to peak concentrations of 49 ppm, 49 ppm, or 49 ppm with four 15-minute exposures to peak concentrations of 98 ppm for 6 hours. The subjects were exposed to each concentration with a 2-week period between each session. The subjects did not have a history of styrene exposure. At the end of the exposure session the subjects were tested for color discrimination (using the Lanthony D-15 desaturated panel), vision contrast, olfactory threshold, simple reaction time, color word stress (response time), symbol digit matching, digit span memory, and continuous tracking. The subjects were also given a questionnaire to assess mood and symptoms. No significant styrene-related alterations in performance on color discrimination, olfactory threshold, neurobehavioral tests, mood, or subjective symptoms were found.

The NOAEL of 49 ppm was selected as the point of departure for the MRL; it was not adjusted for intermittent exposure because the study involved a single exposure for 6 hours. The NOAEL of 49 ppm from the Ska et al. (2003) study was divided by an uncertainty factor of 10 to account for human variability resulting in an acute-duration inhalation MRL of 5 ppm.

Intermediate-Duration Inhalation MRL

No human intermediate-duration studies were identified. Animal studies examining systemic, neurological, reproductive, and developmental toxicity have identified the respiratory tract as the most sensitive target of toxicity. Atrophy of the olfactory epithelium, hypertrophy/hyperplasia of Bowman's gland has been observed in mice exposed to 50 ppm 6 hours/day, 5 days/week for 13 weeks (Cruzan et al. 1997), decreased nasal cilia activity has been observed in rats exposed to 150 ppm 4 hours/day, 5 days/week for 21 days (Ohashi et al. 1986), and focal hyperplasia has been observed in rats exposed to 1,000 ppm 6 hours/day, 5 days/week for 13 weeks (Cruzan et al. 1997). As discussed previously, the mouse does not appear to be a good model for nasal effects in humans due to metabolic differences. Other systemic effects that have been observed include eye irritation in rats exposed to 200 ppm 6 hours/day, 5 days/week for 13 weeks (Cruzan et al. 1997) and centrilobular aggregates of siderophages in the livers of mice exposed to 200 ppm 6 hours/day, 5 days/week for 13 weeks (Cruzan et al. 1997).

A number of studies in rats have reported outer hair cell loss in the organ of Corti in rats exposed to 600–650 ppm for 4 weeks (Loquet et al. 2000; Makitie et al. 2002; Pouyatos et al. 2002) and hearing loss at

750–1,000 ppm for 3–4 weeks (Campo et al. 2001; Lataye et al. 2000, 2001; Loquet et al. 1999, 2000; Pouyatos et al. 2002). A NOAEL of hearing effects of 300 ppm was identified in rats exposed for 12 hours/day, 5 days/week for 4 weeks (Makitie et al. 2002). Other neurological effects include alterations in astroglial cells in rats continuously exposed to 320 ppm for 3 months (Rosengren and Haglid 1989) and decreased sensory nerve conduction velocity in rats exposed to 2,000 ppm 8 hours/day, 5 days/week for 32 weeks (Yamamoto et al. 1997). No reproductive, developmental, or neurodevelopmental effects were observed in a two-generation study (Cruzan et al. 2005a, 2005b); the NOAEL was 500 ppm. In contrast, an increase in neonatal deaths, developmental landmark delays, and alterations in neurochemical levels were observed in the offspring of rats exposed to 300 ppm 6 hours/day on gestational days 6–20 (Katakura et al. 1999, 2001).

Chronic-duration studies suggest that the most sensitive target of styrene toxicity is the nervous system. It is likely that this would also be the most sensitive effect following intermediate-duration exposure. In the absence of human neurotoxicity data, an intermediate-duration inhalation MRL is not recommended at this time.

Chronic-Duration Inhalation MRL

An MRL of 0.2 ppm has been derived for chronic-duration inhalation exposure (greater than 365 days) to styrene.

A large number of occupational exposure studies have examined the toxicity of styrene; however, most of these studies have focused on the potential neurotoxicity of styrene, which appears to be the most sensitive effect. Two common limitations of the occupational exposure studies are: (1) the range of current styrene levels for the workers is typically large and it is difficult to ascribe the observed effects to the mean or median exposure level and (2) historical exposure to higher styrene levels are not adequately taken into consideration. The use of urinary levels of mandelic acid, phenylglyoxylic acid, or mandelic acid plus phenylglyoxylic acid levels as biomarkers for styrene exposure eliminates another common limitation of styrene occupational exposure studies, which is poor characterization of styrene exposure levels due to the lack of personal air samples and the workers' use of respirators with or without canisters.

A variety of neurological effects have been reported in workers at reinforced plastic manufacturing facilities, including decreased color discrimination, slowed reaction time, impaired performance on other neurobehavioral tests, permanent hearing threshold shifts, vestibular effects, altered nerve conduction velocity, and increases in subjective symptoms. A summary of the results of studies for some of these neurological effects is presented in Table 2-1. An alteration in color discrimination is one of the more

consistently found neurological effects; it may also be one of the more sensitive effects. Color discrimination was typically measured using the Lanthony desaturated panel D-15 test in which the subjects were asked to arrange 15 painted caps in a line with definite chromatic sequence; the total color distance score (TCDS) and color confusion index (CCI) are used to quantitatively analyze the results. LOAEL values of 6 to 93 ppm have been identified; however, these LOAELs often reflect the mean exposure level or the lower end of the range of exposure levels. Other neurological effects that have been frequently found include alterations in performance on neurobehavioral tests, particularly reaction time, in workers exposed to ≥21 ppm; vestibular alterations at ≥18 ppm; and increased frequency of clinical symptoms (e.g., tiredness and headaches in workers exposed to ≥6 ppm). Hearing loss and alterations in nerve conduction velocity have also been reported in some studies, but the finding is not consistent across studies.

Non-neurological effects observed in styrene workers include obstructive lung effects (Chmielewski and Renke 1975), mild hematological alterations (Checkoway and Williams 1982; Stengel et al. 1990; Thiess and Friedheim 1978), and impaired immune response to concanavalin (Somorowská et al. 1999; Tulinska et al. 2000). Although exposure levels were not reported in all of these studies, effects were typically observed at styrene concentrations of >20 ppm. Clinical chemistry studies did not find alterations indicative of impaired liver (Härkönen et al. 1984; Hotz et al. 1980; Lorimer et al. 1978; Thiess and Friedheim 1978) or kidney (Verplanke and Herber 1998; Viau et al. 1987; Vyskocil et al. 1989) function in workers exposed to ≥24 ppm.

Chronic-duration studies in laboratory animals identify the nasal olfactory epithelium as the most sensitive end point. Atrophic and/or degenerative changes were observed in rats exposed to 50 ppm styrene 6 hours/day, 5 days/week for 104 weeks (Cruzan et al. 1998) and respiratory metaplasia in the nasal olfactory epithelium were observed in mice exposed to 20 ppm 6 hours/day, 5 days/week for 98–104 weeks (Cruzan et al. 2001). As noted previously, mice do not appear to be a good model for potential respiratory effects in humans.

Alterations in color discrimination and reaction time are two neurological effects consistently found in styrene workers. Benignus et al. (2005) conducted a meta-analysis using color discrimination impairment data from the Campagna et al. (1996), Eguchi et al. (1995), Gobba et al. (1991), Gong et al. (2002), and Kishi et al. (2001) studies and choice reaction time data from the Jegaden et al. (1993), Mutti et al. (1984a), Triebig et al. (1989), and Tsai and Chen (1996) studies. Average styrene exposure

Table 2-1. Results of Selected Human Neurotoxicity Studies

Result	Reference	NOAEL ppm	LOAEL ppm
Decreased color discrimination	Chia et al. 1994		6
	Kishi et al. 2001	4	10
	Gong et al. 2002		10
	Gobba et al. 1991		16
	Triebig et al. 2001		20
	Iregren et al. 2005		22
	Fallas et al. 1992		24.3
	Campagna et al. 1996		26
	Eguchi et al. 1995	8	93
Neurological symptoms	Flodin et al. 1989	6	
	Edling et al. 1993	8.6	
	Checkoway et al. 1992	10.8	18.9
	Cherry et al. 1980		92
Vestibular effects	Möller et al. 1990		18
	Toppila et al. 2006		24.8
	Calabrese et al. 1996		36
Reaction time	Edling et al. 1993	8.6	
	Tsai and Chen 1996		21.9
	Jegaden et al. 1993		22.68
	Fallas et al. 1992		24.3
	Mutti et al. 1984a		25
	Gamberale et al. 1976		47
	Cherry et al. 1980		92
Hearing	Morata et al. 2002		3.68
	Śliwińska-Kowalska et al. 2003		15.6
	Morioka et al. 1999		16
	Möller et al. 1990	18	
	Calabrese et al. 1996	36	
	Triebig et al. 2009	40	50
Nerve conduction velocity	Seppäläinen and Härkönen 1976	30	
	Štětkářová et al. 1993		50
	Triebig et al. 1985	100	

concentrations were estimated from individual data reported in the papers; for studies reporting individual data as urinary mandelic acid levels, standardized methods for converting to styrene exposure levels were used. Cumulative styrene exposure was estimated by multiplying exposure level by length of employment. A common metric of effect magnitude (percentage of baseline) was calculated for the different neurological effects. The analysis found a significant linear relationship between choice reaction time and cumulative styrene exposure; cumulative exposure accounted for 91% of the variance in reaction time. Similarly, a significant relationship between CCI and cumulative styrene exposure was found, with cumulative exposure accounting for 35% of the variance in CCI. Using the regression equations for these two effects, Benignus et al. (2005) estimated that exposure to 150 ppm for 8 work-years would result in a 50% increase in choice reaction time and a 17% increase in CCI score; exposure to 20 ppm for 8 work-years would result in a 6.5% increase in choice reaction time and a 2.23% increase in CCI score. As discussed in Benignus et al. (2005), a 7% decrease in reaction time would prevent 58,000–70,000 injuries per year from automobile accidents. The investigators also noted that CCI increases with age, and the rate of increase is about 10% per 13 years of age; thus, a 2.23% decrease in color perception would be roughly equivalent to 2.9 additional years of age. Based on this analysis, 20 ppm is considered a LOAEL for neurological effects.

In addition to the studies included in the Benignus et al. (2005) meta-analysis, a LOAEL of 20 ppm is supported by a color discrimination study conducted by Triebig et al. (2001). In this study, significant increases in CCI values were observed in styrene workers with urinary mandelic acid plus phenylglyoxylic acid levels of ≥472 mg/g creatinine (approximately 20 ppm air styrene concentration), when compared to >95th percentile age-dependent reference CCI values. An advantage of the Triebig et al. (2001) study is that individual exposure and CCI data were reported, which diminishes the problem of ascribing an observed effect to the mean or median concentration and the study addresses the issue of biological relevance because the CCI scores were compared to the 95th percentile of age-dependent reference values rather than values in the control group.

In comparisons between styrene workers and a control group employed at the same facility without styrene exposure, Triebig et al. (2001) found no significant differences in CCI scores between workers and controls when the tests were conducted on a Monday morning, but CCI scores were significantly different when measured on a Thursday afternoon. Within the styrene-exposed workers, CCI scores on Monday morning and Thursday afternoon were not significantly different. After a 4-week nonexposure period, the CCI scores were significantly reduced in the styrene workers. After styrene exposure levels were lowered, no difference between workers and controls was observed on Monday morning or

Thursday afternoon. However, among styrene workers, there were significant differences between Monday morning and Thursday afternoon measurements and between Monday morning and post-vacation levels. These findings provide suggestive evidence that the alterations in color discrimination were reversible.

The LOAEL of 20 ppm identified in the Benignus et al. (2005) meta-analysis was selected as the point of departure for the chronic-duration inhalation MRL. The LOAEL was adjusted for intermittent exposure (8 hours/day, 5 days/week) and divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability), resulting in a chronic-duration inhalation MRL of 0.2 ppm. The LOAEL was classified as a minimal LOAEL based on the findings of Triebig et al. (2001) that alterations in color vision were reversible and the workers were not aware of any changes in color vision.

Oral MRLs

Acute-Duration Oral MRL

An MRL of 0.1 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to styrene.

A limited number of studies have examined the acute toxicity of orally administered styrene; these studies have examined potential neurotoxicity and developmental toxicity. No developmental effects were observed in rats administered a single dose of 300 mg/kg on gestational day 11 (Daston et al. 1991) or administered 300 mg/kg/day (administered as two daily doses of 150 mg/kg) on gestational days 6–15 (Murray et al. 1978). Impaired learning was observed in rats administered via gavage 100 or 200 mg/kg/day for 14 days; increases in serotonin levels were observed in the hypothalamus, hippocampus, and midbrain (Husain et al. 1985). In another study, increases in dopamine receptor binding was observed in rats administered a single gavage dose of 200 mg/kg (Agrawal et al. 1982).

Although a limited number of toxicity end points have been examined following acute-duration oral exposure, longer-term oral studies examining systemic and reproductive end points have identified LOAELs that were higher than the 100 mg/kg/day LOAEL identified for neurotoxicity in the Husain et al. (1985) study. The lowest LOAEL identified for a systemic effect is 400 mg/kg/day for Heinz body formation in dogs administered styrene by gavage for 561 days (Quast et al. 1979); the NOAEL was 200 mg/kg/day. Decreased spermatozoa counts were observed in adult rats administered 400 mg/kg 6 days/week for 60 days (Srivastava et al. 1989), young rats exposed via lactation on postnatal days 1–

21 (maternal dose of 400 mg/kg/day) (Srivastava et al. 1992a), and young rats administered 200 mg/kg 6 days/week on postnatal days 1–61 (Srivastava et al. 1992b); the NOAELs identified in these three studies were 200, 200, and 100 mg/kg, respectively. Marked degeneration of the seminiferous tubules was also observed in the adult rats administered 400 mg/kg (Srivastava et al. 1989). Impaired learning observed in rats administered 500 mg/kg 5 days/week for 8 weeks (no NOAEL identified) (Bushnell 1994) also supports the identification of neurotoxicity as a sensitive end point following oral exposure. Additionally, the extensive inhalation toxicity database for styrene supports the selection of neurotoxicity as the most sensitive target of toxicity; both the acute- and chronic-duration inhalation MRLs are based on neurological effects in humans. Neurological effects observed in chronically exposed styrene workers include decreased color discrimination, slowed reaction time, increased prevalence of neurological symptoms, and ototoxicity (hearing and vestibular effects).

The Husain et al. (1985) study was selected as the basis of the acute-duration oral MRL. In this study, groups of 15 male Wistar rats were administered by gavage 0, 100, or 200 mg/kg/day styrene in ground nut oil for 14 consecutive days. Spontaneous motor activity with or without amphetamine induction was observed 1 day after the last dose. Two days after exposure termination, the rats underwent acquisition training for 4 days. Learning was assessed by measuring the number of times the rat climbed the pole after the conditioned stimulus to avoid the foot-shock unconditioned stimulus. Noradrenaline, dopamine, and serotonin levels were measured in seven regions of the brain in six rats/group sacrificed after the acquisition training. No overt signs of toxicity were observed. No significant alterations in locomotor activity were observed with or without amphetamine induction. Significantly greater increases in percent avoidance response in the conditioned avoidance response test (indicative of impaired learning) were observed at 100 and 200 mg/kg/day; no difference was found between the two styrene groups. The effects were observed on test day 3 and 4. Significant increases in the level of serotonin in the hypothalamus (70%), hippocampus (51%), and midbrain (29%) were observed at 200 mg/kg/day. Styrene exposure did not affect brain noradrenaline and dopamine levels.

The LOAEL of 100 mg/kg/day was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Intermediate-Duration Oral MRL

The systemic toxicity of styrene has not been investigated in intermediate-duration oral exposure studies. Neurotoxicity studies have identified a LOAEL of 200 mg/kg/day for increased dopamine receptor

binding in rats (Agrawal et al. 1982), a LOAEL of 500 mg/kg (5 days/week) for impaired learning in rats (Bushnell 1994), and a LOAEL of 906 mg/kg/day for alterations in serotonin and noradrenaline levels in rats (Husain et al. 1980); none of these studies identified a NOAEL for neurological effects. An increase in dopamine receptor binding was also observed in the offspring of rats administered 200 mg/kg/day during gestation, lactation, or both (Zaidi et al. 1985). Reproductive and immunological effects were reported in the other intermediate-duration oral studies. Decreases in spermatozoa counts were observed in rats exposed as 400 mg/kg (6 days/week) as adults, 200 mg/kg (6 days/week) as neonates, or during lactation (maternal dose of 400 mg/kg/day) (Srivastava et al. 1989, 1992a, 1992b). Impaired immune function was observed in mice exposed to 30 mg/kg/day and in rats exposed to 294 mg/kg/day (Dogra et al. 1992); the NOAELs were 23 and 196 mg/kg/day.

Dogra et al. (1992) identified the lowest LOAEL following intermediate-duration oral exposure to styrene; however, there are limited data to support the identification of the immune system as a sensitive, relevant target for humans. Although, the sensitivity of the nervous system has been firmly established following inhalation and oral exposure, the LOAELs identified in the intermediate-duration studies are higher than the lowest LOAEL for neurotoxicity identified in an acute-duration study (Husain et al. 1985). An MRL based on the Dogra et al. (1992) study would be higher than the acute-duration oral MRL; thus, an intermediate-duration MRL is not recommended at this time.

Chronic-Duration Oral MRL

The available data on the chronic toxicity of styrene comes from three systemic toxicity studies. No adverse effects were observed in rats exposed to 35 mg/kg/day styrene in drinking water for 2 years (Beliles et al. 1985) and no liver or kidney alterations were observed in rats administered 500 mg/kg 1 day/week for 120 weeks (Ponomarkov and Tomatis 1978). Increase in Heinz body formation was observed in dogs administered 400 mg/kg/day for 561 days (Quast et al. 1979); the NOAEL for this effect is 200 mg/kg/day.

The chronic-duration inhalation database provides strong evidence that neurotoxicity is the most sensitive target of styrene toxicity. It is not known if this would also be true for chronic-duration oral exposure; the acute-toxicity oral database provides suggestive evidence that it would be a sensitive target. In the absence of a long-term oral study examining neurological end points, a chronic-duration oral MRL is not recommended.

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 styrene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

3.2.1 Inhalation Exposure

Most information on the effects of inhalation exposure to styrene in humans comes from studies of workers exposed to styrene vapors in the production and use of plastics and resins, especially polyester resins dissolved in styrene. In most cases, the studies involve workplace exposures such as fiberglass boat building factories where the actual levels of styrene are reported as a range of styrene air concentrations. However, there are a few human clinical studies in which exposures are better quantified. A common limitation of many of the occupational exposure studies is the phenomenon of the healthy worker effect. The selection of healthy individuals for employment and the likelihood that more susceptible workers are more likely to leave the workforce can result in workers who are healthier than the general population. This type of bias typically affects comparisons with the general population and is less likely to influence comparisons with other groups of workers. Provided below are descriptions of the known effects of inhalation exposure of humans and animals to styrene.

3.2.1.1 Death

There have been no reports of deaths in humans directly associated with exposure to styrene in the workplace (EPA 1985a; Gosselin et al. 1984; NIOSH 1983).

In animals, inhalation studies indicate that the acute toxicity of styrene is low to moderate. An LC_{50} of 2,770 ppm after 2 hours of exposure was reported in rats, and the LC_{50} for mice after exposure for 4 hours was 4,940 ppm (Shugaev 1969). All rats and guinea pigs survived after exposure to 1,300 ppm styrene

for 30 hours and 16 hours, respectively (Spencer et al. 1942). However, all animals died after 40 hours of exposure. Gender differences in mortality were observed in repeated-exposure studies (6 hours/day, 5 days/week for 2 weeks) (Cruzan et al. 1997). Increases in mortality were observed in female CD-1 and B6C3F1 female mice exposed to 250 ppm; no deaths were observed at 500 ppm. In the CD-1 and B6C3F1 males, very few deaths were observed at 250 ppm, but increases in deaths were observed at 500 ppm. A similar finding was reported by Morgan et al. (1993a): increases in mortality were observed in female B6C3F1 mice exposed to 250 ppm and no deaths were observed at 500 ppm; in males, deaths were observed at 250 and 500 ppm. In contrast to these findings, no deaths were observed in Sprague Dawley rats exposed to concentrations as high as 1,500 ppm 6 hours/day, 5 days/week for 13 weeks (Cruzan et al. 1997).

All reliable LOAEL values and LC_{50} values for lethality in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding dermal or metabolic effects in humans or animals after inhalation exposure to styrene.

For the following systemic effects resulting from inhalation exposure to styrene, the highest NOAEL values and all reliable LOAEL values in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Several human studies have examined the respiratory effects caused by inhalation exposure to styrene. The most commonly reported general symptom is mucous membrane irritation. Irritation of the upper respiratory tract (i.e., nose and throat) has been reported by volunteers (Carpenter et al. 1944; Stewart et al. 1968) and workers (NIOSH 1983). Throat irritation and increased nasal secretion occurred following exposure of two male subjects to 800 ppm for 4 hours (Carpenter et al. 1944). Nasal irritation was observed in all volunteers after exposure to 376 ppm styrene for 60 minutes (Stewart et al. 1968). Obstructive lung changes were observed in 4 of 21 workers exposed to styrene for about 10 years (Chmielewski and Renke 1975). However, exposure levels were not defined. No histological alterations were observed in nasal biopsies from styrene workers exposed to 50–60 ppm styrene for 7 years (Ödkvist et al. 1985).

Table 3-1 Levels of Significant Exposure to Styrene - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat	3-40 hr				1300 (100% mortality after >40 hours exposure)	Spencer et al. 1942 Styrene	
2	Mouse (CD-1 and B6C3F1)	6 hr/d 5 d/wk 2 wk				250 (increased mortality)	Cruzan et al. 1997 Styrene	
3	Mouse (B6C3F1)	6 hr/d 14 d				250 M (44% mortality)	Morgan et al. 1993a Styrene	
4	Gn Pig	3-40 hr				1300 (100% mortality after 40 hours exposure)	Spencer et al. 1942 Styrene	
Systemic								
5	Human	7 hr	Ocular		99 M (mild, transient eye irritation)		Stewart et al. 1968 Styrene	
6	Human	1 or 2 hr	Resp	216 M	376 M (nasal irritation)		Stewart et al. 1968 Styrene	
			Ocular	216 M	376 M (eye irritation)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
7	Mouse (CD-1 and B6C3F1)	6 hr/d 5 d/wk 2 wk	Resp		250 (shallow breathing)		Cruzan et al. 1997 Styrene	
			Hepatic	60	250 (increased liver weight and centrilobular hepatocyte necrosis)			
8	Mouse (CD-1)	6 hr/d 3 d	Resp		80 M (single cell necrosis in nasal olfactory epithelium)		Cruzan et al. 2001 Styrene	
9	Mouse (CD-1)	6 hr/d 3 d	Resp	40 M	160 M (moderate to marked degenerative changes in olfactory epithelium)		Green et al. 2001a Styrene	
10	Mouse (B6C3F1)	6 hr/d 14 d	Hepatic	125	250 M (pigmented macrophages and focal necrosis)		Morgan et al. 1993a Styrene	
			Renal	500				
			Bd Wt	500				
11	Mouse (B6C3F1)	6 hr/d 1-3 d	Hepatic			250 M (mild to marked necrosis)	Morgan et al. 1993a Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
12	Mouse (B6C3F1)	6 hr/d 3 d	Hepatic	125		250 (severe hepatocellular degeneration/necrosis)	Morgan et al. 1993b Styrene	
13	Mouse	6 hr/d 4 d	Hepatic	125		250 (marked degeneration and/or coagulative necrosis of centrilobular hepatocytes)	Morgan et al. 1993c Styrene	
Immuno/ Lymphoret								
14	Mouse (BALB/c)	6 hr/d 4 d			100 F (exacerbated inflammatory reaction after ovalbumin challenge)		Ban et al. 2006 Styrene	
Neurological								
15	Human	1 hr			87 (inhibition of vestibular-oculomotor system)		Odkvist et al. 1982 Styrene	
16	Human	3 or 4 hr		20			Seeber et al. 2004 Styrene	
17	Human	6 h		49 M[b]			Ska et al. 2003 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
18	Human	1 or 2 hr		216 M	376 M (impaired performance on balance and coordination tests)		Stewart et al. 1968 Styrene	
19	Human	7 hr		99 M			Stewart et al. 1968 Styrene	
20	Rat (Long- Evans)	6 hr/d 5 d/wk 1 or 2 wk				1000 M (hearing loss and loss of OHC)	Campo et al. 2001 Styrene	
21	Rat (Long- Evans)	8 hr/d 5 d				1600 M (hearing loss at 8 and 16 kHz)	Crofton et al. 1994 Styrene	
22	Rat (Long- Evans)	6 hr/d 5 d				1000 M (hearing loss, loss of OHC)	Lataye et al. 2003 Styrene	
23	Mouse (CD-1 and B6C3F1)	6 hr/d 5 d/wk 2 wk		60		250 (lethargy and unsteady gait)	Cruzan et al. 1997 Styrene	
24	Mouse (Swiss OF1)	4 hr		413 M	610 M (impaired performance on a swimming test)		De Ceaurriz et al. 1983 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
25	Gn Pig (NS)	6 hr/d 5 d		1000 M			Lataye et al. 2003 Styrene	
Reproductive								
26	Mouse	5 d 5 hr/d		300 M			Salomaa et al. 1985 Styrene	
Developmental								
27	Rat (Sprague-Dawley)	7 hr/d Gd 6-15		600 F			Murray et al. 1978 Styrene	
28	Mouse (BMR/T6T6)	6 hr/d Gd 6-16		250 F			Kankaanpaa et al. 1980 Styrene	
29	Hamster (Chinese)	6 hr/d Gd 6-18		750 F		1000 F (fetal deaths or resorptions)	Kankaanpaa et al. 1980 Styrene	
30	Rabbit (New Zealand)	7 hr/d Gd 6-18		600 F			Murray et al. 1978 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
31	Rat (Sprague-Dawley)	6 hr/d 5 d/wk 13 wk	Resp	500	1000 (focal hyperplasia in nasal olfactory epithelium)		Cruzan et al. 1997 Styrene	
			Hemato	1500				
			Hepatic	1500				
			Renal	1500				
			Ocular		200 (eye irritation)			
			Bd Wt	1000 M	1500 M (10% decrease in body weight gain)			
32	Rat (Long- Evans)	6 hr/d 5 d/wk 4 wk	Hepatic	750 M			Loquet et al. 2000 Styrene	Urinary markers of renal toxicity and serum markers of liver toxicity.
			Renal	750 M				
33	Rat	21 d 5 d/wk 4 hr/d	Resp		150 M (decreased nasal cilia activity)	1000 M (disabled nasal cilia activity)	Ohashi et al. 1986 Styrene	
34	Rat (Sprague-Dawley)	13 wk 5 d/wk 7 hr/d	Renal	133			Viau et al. 1987 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
35	Rat (Wistar)	8 hr/d 5 d/wk 32 wk	Bd Wt	200 M	2000 M (>15% decrease in body weight gain)		Yamamoto et al. 1997 Styrene	
36	Rat (Fischer- 344)	14 hr/d 5 d/wk 3 wk	Bd Wt		800 M (10-13.5% decrease in body weight)		Yano et al. 1992 Styrene	
37	Mouse (CD-1)	6 hr/d 5 d/wk 13 wk	Resp		50 (atrophy of olfactory epithelium, dilatation, hypertrophy, hyperplasia of Bowman's gland; decreased eosinophilia of bronchiolar epithelial cells)		Cruzan et al. 1997 Styrene	
			Hemato	200				
			Hepatic	100 F	150 F (centrilobular aggregates of siderphages)			
			Bd Wt	150 M	200 M (decreased body weight gain)			
38	Pig	3 wk 5 d/wk 6 hr/d	Hemato	360			Johnston et al. 1983 Styrene	
Neurological								
39	Rat (Long- Evans)	6 hr/d 5 d/wk 3 or 4 wk				1000 M (hearing loss, loss of OHC in organ of Corti)	Campo et al. 2001 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
40	Rat (Long- Evans)	6 hr/d 5 d/wk 4 wk				750 M (hearing loss and loss of OHC)	Lataye et al. 2000 Styrene	
41	Rat (Long- Evans)	6 hr/d 5 d/wk 4 wk				1000 M (loss of OHC and spiral ganglion cell density in organ of Corti)	Lataye et al. 2001 Styrene	
42	Rat (Long- Evans)	6 hr/d 5 d/wk 4 wk			650 M (OHC loss)	850 M (hearing loss and loss of OHC)	Loquet et al. 1999 Styrene	
43	Rat (Long- Evans)	6 hr/d 5 d/wk 4 wk				750 M (hearing loss and loss of OHC)	Loquet et al. 2000 Styrene	
44	Rat (Wistar)	12 hr/d 5 d/wk 4 wk		300 M	600 M (hearing impairment and loss of OHC)		Makitie et al. 2002 Styrene	
45	Rat (Long- Evans)	6 hr/d 5 d/wk 4 wk			650 M (OHC loss)	750 M (hearing loss and OHC loss)	Pouyatos et al. 2002 Styrene	
46	Rat (Fischer- 344)	3 wk 14 hr/d				800 M (hearing loss)	Pryor et al. 1987 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
47	Rat (Sprague-Dawley)	3 mo continuous		90 M	320 M (astroglial alterations)		Rosengren and Haglid 1989 Styrene	
48	Rat (Wistar)	8 hr/d 5 d/wk 32 wk		200 M	2000 M (decreased sensory nerve conduction velocity)		Yamamoto et al. 1997 Styrene	
49	Rat (Fischer- 344)	14 hr/d 5 d/wk 3 wk				800 M (hearing loss and loss of OHC in organ of Corti)	Yano et al. 1992 Styrene	
50	Mouse (CD-1)	6 hr/d 5 d/wk 13 wk		50	100 (atrophy of olfactory nerve fibers)	200 F (transient lethargy, cold to touch, and slow respiration)	Cruzan et al. 1997 Styrene	
Reproductive								
51	Rat (CD)	6 hr/d 70 pmd 14 d mating Gd 0-21 Ld 5-21		500			Cruzan et al. 2005a, 2005b Styrene	
Developmental								
52	Rat (CD)	6 hr/d 70 pmd 14 d mating Gd 0-21 Ld 5-21		500			Cruzan et al. 2005a, 2005b Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
53	Rat (Wistar)	6 hr/d Gd 6-20				300	(increased neonatal deaths, delays in righting reflex and incisor eruption, alterations in neurochemical levels)	Katakura et al. 1999, 2001 Styrene	
CHRONIC EXPOSURE									
Systemic									
54	Human	5.1 yr (Occup)	Hepatic	40 F				Harkonen et al. 1984 Styrene	
55	Human	7 yr (Occup)	Resp	46 M				Odkvist et al. 1985 Styrene	
56	Human	12.6 yr (Occup)	Renal	26				Verplanke et al. 1998 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
57	Rat (Sprague-Dawley)	6 hr/d 5 d/wk 104 wk	Resp		50 (atrophic and/or degenerative changes in nasal olfactory epithelium)		Cruzan et al. 1998 Styrene	
			Cardio	1000				
			Gastro	1000				
			Hemato	1000				
			Hepatic	1000				
			Renal	1000				
			Ocular	1000				
			Bd Wt	200 F	500 F (decreased body weight gain)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
58	Mouse (CD-1)	6 hr/d 5 d/wk 98-104 wk	Resp		20 (respiratory metaplasia in nasal olfactory epithelium, bronchiolar epithelial hyperplasia)		Cruzan et al. 2001 Styrene	
			Cardio	160				
			Gastro	160				
			Hemato	160				
			Hepatic	160				
			Renal	160				
			Ocular	160				
			Bd Wt	80 M	160 M (11% decrease in body weight gain)			
Immuno/ Lymphoret								
59	Human	7 yr (Occup)			30 (alterations in lymphocyte subsets)		Bergamaschi et al. 1995b Styrene	
60	Human	13 yr (Occup)			26 (impaired immune response to concanavalin A)		Tulinska et al. 2000 Styrene	
Neurological								
61	Human	(Occup)			20[c] (decreased color discrimination and reaction time)		Benignus et al. 2005 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
62	Human	7.6 yr (Occup)			36 (altered performance vestibular tests)		Calabrese et al. 1996 Styrene	
63	Human	62.5 or 79.3 mo (Occup)			26 (decreased color discrimination)		Campagna et al. 1996 Styrene	
64	Human	4-6.4 yr (Occup)		10.8	18.9 (increased prevalence of neurological symptoms)		Checkoway et al. 1992 Styrene	
65	Human	(Occup)			92 M (tiredness, slow reaction times, mood changes)		Cherry et al. 1980 Styrene	
66	Human	18.8 yr (Occup)			6 M (decreased color discrimination and performance on neurobehavioral tests)		Chia et al. 1994 Styrene	
67	Human	12.5 yr (Occup)		24.6			Dalton et al. 2003 Styrene	
68	Human	9 yr (Occup)			8.6 M (increased symptoms of neurotoxicity)		Edling et al. 1993 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
69	Human	7.0 yr (Occup)		8 M	93 M (decreased color discrimination)		Eguchi et al. 1995 Styrene	
70	Human	6.5 yr (Occup)			24.3 M (decreased color discrimination)		Fallas et al. 1992 Styrene	
71	Human	2.7 yr (Occup)			47 M (slowed reaction time)		Gamberale et al. 1976 Styrene	
72	Human	(Occup)			16 (decreased color discrimination)		Gobba et al. 1991 Styrene	
73	Human	76.6 mo (Occup)			10 M (decreased color discrimination)		Gong et al. 2002 Styrene	
74	Human	12.9-17.8 yr (Occup)			22 M (decreased color discrimination)		Iregren et al. 2005 Styrene	
75	Human	5 yr (Occup)			22.68 (impaired performance on neurobehavioral tests of visual reaction and memory)		Jegaden et al. 1993 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
76	Human	6.2 yr (Occup)		4	10 (decreased color discrimination)		Kishi et al. 2001 Styrene	
77	Human	4.9 yr (Occup)			75 M (impaired performance on visuomotor accuracy and psychomotor performance tests)		Lindstrom et al. 1976 Styrene	
78	Human	10.8 yr (Occup)			18 M (impaired vestibular function)		Moller et al. 1990 Styrene	
79	Human	17 yr (Occup)		3.68			Morata et al. 2002 Styrene	
80	Human	9.4 yr (Occup)			16 M (reduction in upper limit of hearing)		Morioka et al. 1999 Styrene	
81	Human	5 yr (Occup)			22 M (slowed distribution of nerve conduction velocities and ECG R-R interval)		Murata et al. 1991 Styrene	
82	Human	8.6 yr (Occup)			25 (decreased verbal learning skills)		Mutti et al. 1984a Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
83	Human	6.4 years (mean)			15.9 M (increased vibration perception threshold)		Sato et al. 2009 Styrene	
84	Human	5 yr (Occup)			30 M (EEG abnormalities)		Seppalainen and Harkonen 1976 Styrene	
85	Human	(Occup)			15.6 (hearing loss)		Sliwinska-Kowalska et al. 2003 Styrene	
86	Human	11 yr (Occup)			50 F (decreased peripheral nerve conduction velocity and prolonged latency of somatosensory evoked potentials)		Stetkarova et al. 1993 Styrene	
87	Human	(Occup)			24.8 M (impaired postural stability)		Toppila et al. 2006 Styrene	
88	Human	4 yr		100 M			Triebig et al. 1985 Styrene	Measured nerve conduction velocity.
89	Human	4.5 years (Occup)			20 M (impaired color vision)		Triebig et al. 2001 Styrene	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
90	Human	mean of 5.7-6.3 years (Occup)			50 M (increased hearing threshold in workers exposed to high concentrations for long durations)		Triebig et al. 2009 Styrene	
91	Human	8.3 yr (Occup)			21.9 (impaired performance on neurobehavioral tests)		Tsai and Chen 1996 Styrene	
Developmental								
92	Human	>1 yr 7 d/wk 8 hr/d		82 F			Lemasters et al. 1989 Styrene	
Cancer								
93	Mouse (CD-1)	6 hr/d 5 d/wk 98-104 wk				160 F (CEL: bronchioloalveolar carcinoma)	Cruzan et al. 2001 Styrene	

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

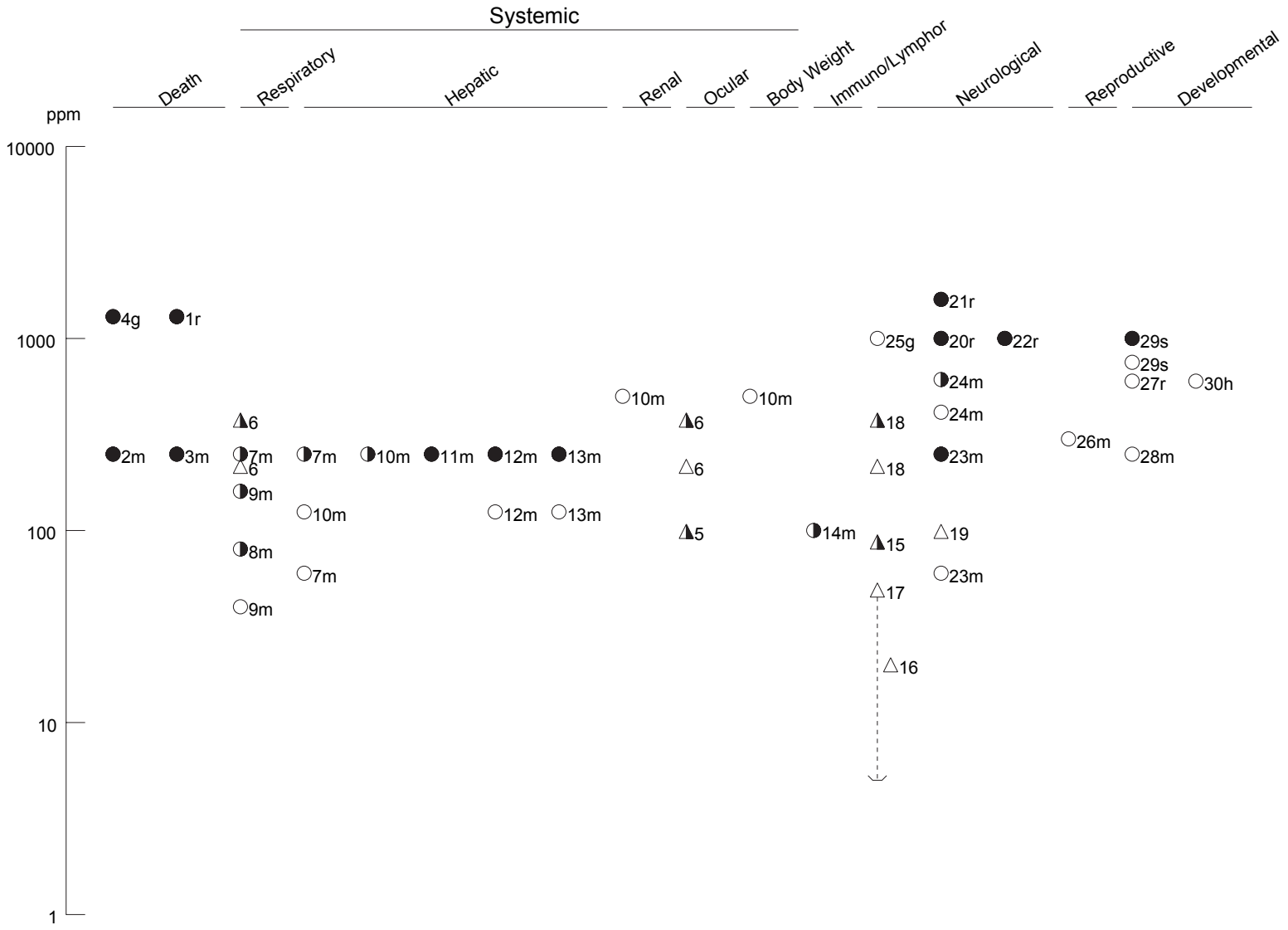
b The acute-duration inhalation MRL of 5 ppm was calculated based on NOAEL of 49 ppm and divided by an uncertainty factor of 10 to account for human variability.

c The chronic-duration inhalation MRL of 0.2 ppm was calculated from a minimal LOAEL of 20 ppm identified in a meta-analysis of occupational exposure studies reporting significant alterations in color discrimination and choice reaction time; the LOAEL was adjusted for intermittent exposure (8 hours/day, 5 days/week) and divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); ECG = electrocardiographic; F = Female; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); kHz = kilohertz; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; OHC = outer hair cell(s); pmd = pre-mating day; ppm = parts per million; Resp = respiratory; x = time(s); wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Styrene - Inhalation

Acute (≥14 days)



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

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

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

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

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

Intermediate (15-364 days)

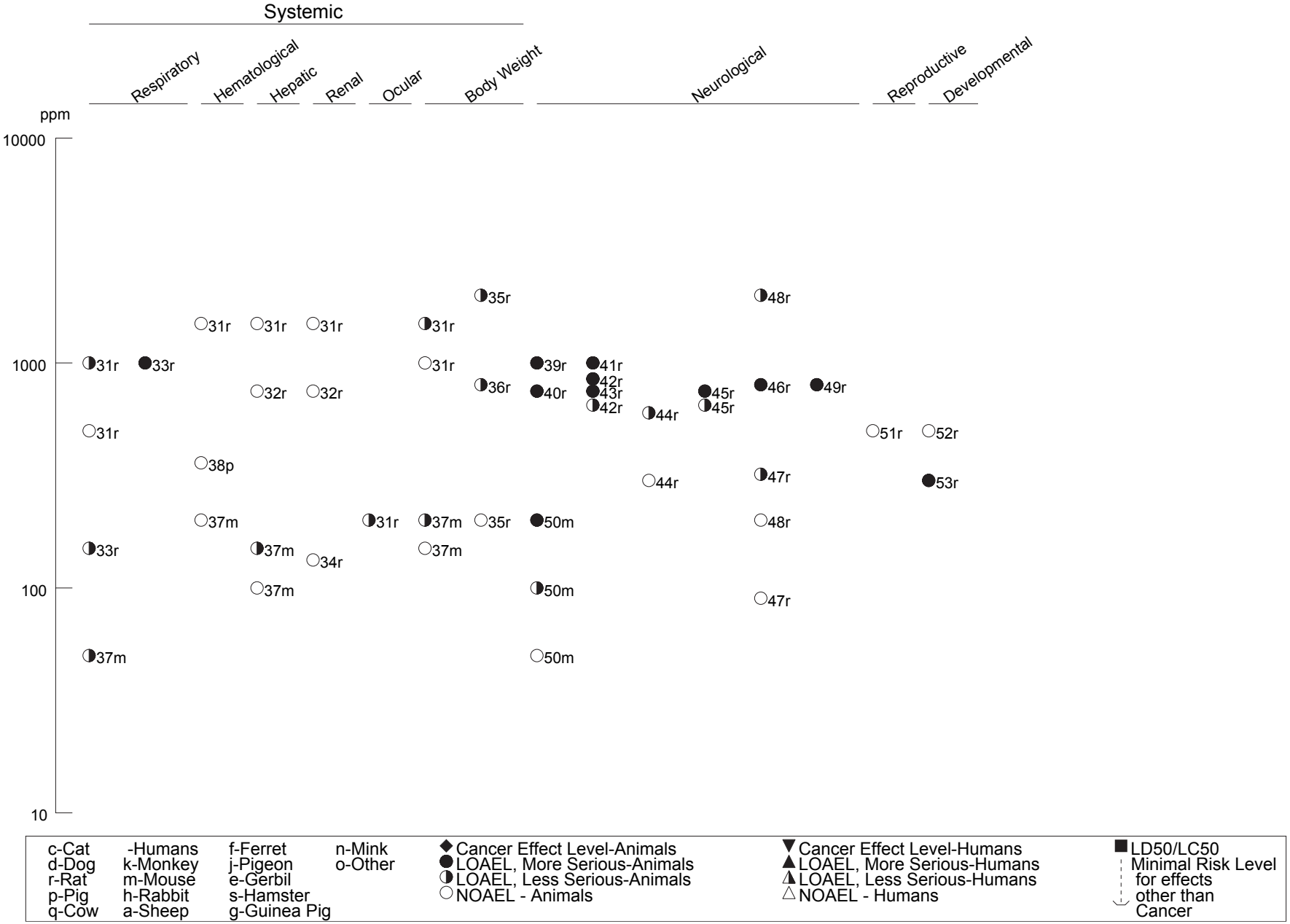
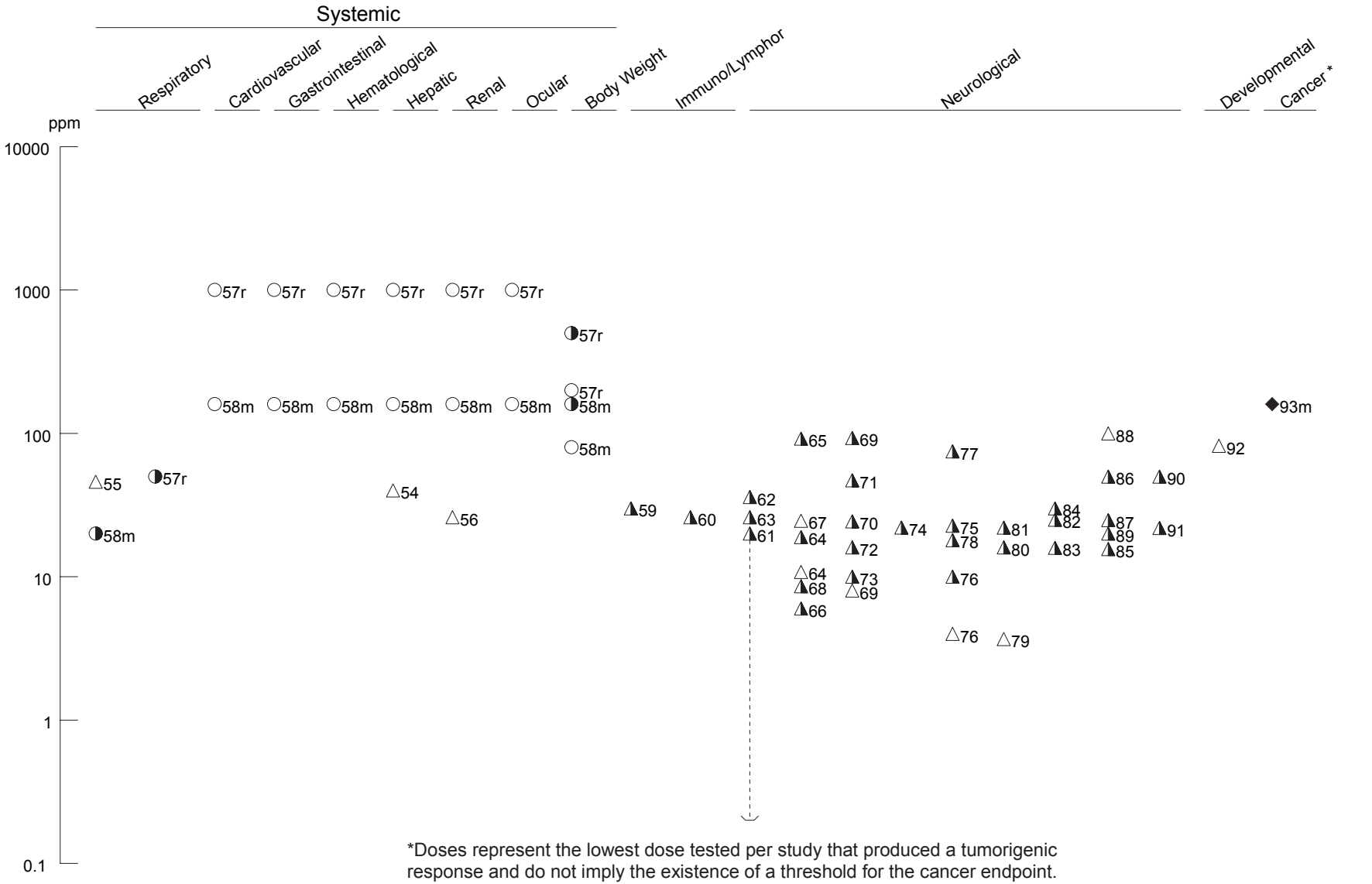


Figure 3-1 Levels of Significant Exposure to Styrene - Inhalation *(Continued)*

Chronic (≥365 days)



In rats exposed to 150 ppm styrene 4 hours/day, 5 days/week for 3 weeks a decrease in nasal ciliary activity was observed; at 1,000 ppm, the nasal cilia activity was considered disabled (Ohashi et al. 1986). Electron microscopic examination of the nasal cavity of rats exposed to 1,000 ppm revealed very few ciliated cells and severe degeneration with marked vacuolization. Decreases in cilia activity were also observed in the trachea at 150 and 1,000 ppm. After a 12-week recovery period, nasal and tracheal cilia activity in the 150 ppm group was similar to controls; nasal cilia activity in the 1,000 ppm group was still lower than controls but was increased compared to rats killed at the end of the exposure period (Ohashi et al. 1986). In a longer-term study, focal hyperplasia was observed in the nasal olfactory epithelium of rats exposed to 1,000 ppm for 13 weeks (Cruzan et al. 1997); at 500 ppm, no histological alterations were observed in the respiratory tract. Chronic exposure to 50 ppm resulted in atrophic and/or degenerative changes in the nasal olfactory epithelium (Cruzan et al. 1998).

Mice appear to be more sensitive than rats to the respiratory toxicity of styrene. Exposure to 50 ppm styrene for 13 weeks resulted in atrophy of the nasal olfactory epithelium and dilatation, hypertrophy and hyperplasia of Bowman's gland (Cruzan et al. 1997). At 100 ppm, atrophy of the nasal olfactory nerve fibers was observed; focal crowding of nonciliated epithelial cells in the bronchioles were observed at 150 ppm. Chronic exposure resulted in respiratory metaplasia of the nasal olfactory epithelium and dilatation, respiratory metaplasia, epithelial hyperplasia of the Bowman's gland in mice exposed to ≥20 ppm for 2 years (Cruzan et al. 2001). Decreased eosinophilia of epithelial cells and bronchiolar epithelial hyperplasia were observed in the lungs of mice exposed to ≥20 ppm.

A study by Spencer et al. (1942) also provides some information on species differences. Rats and guinea pigs exposed 1,300 ppm for 7–8 hours/day, 5 days/week for 6 months showed nasal irritation, but rabbits and monkeys did not (Spencer et al. 1942). Histopathological examinations revealed no changes between test and control rats, but pronounced lung irritation was seen in guinea pigs that died after a few exposures. The irritation, which included congestion, hemorrhages, edema, exudation, and a general acute inflammatory reaction, was not seen in the guinea pigs, rabbits, and monkeys that survived the 6-month exposure period (Spencer et al. 1942).

Green et al. (2001a) suggest that the observed species differences between mice and rats are due to differences in styrene metabolism in the nasal epithelium. The rates of metabolism of styrene by cytochromes P-450 CYP2E1 and CYP2F2 to styrene oxide was similar for the two species. However, styrene oxide is more efficiently metabolized by epoxide hydrolases and glutathione S-transferases in rats than in mice. Thus, the higher levels of the reactive epoxide styrene oxide in mice is the likely cause of

the increased sensitivity in this species. In *in vitro* assays in fresh human nasal tissues, styrene oxide was not detected and high levels of epoxide hydrolases were detected, suggesting that humans have limited capacity to metabolize styrene in the nasal cavity and a high potential to detoxify styrene oxide. These data suggest that rodents may not be a good model for nasal toxicity in humans.

These well-conducted human and animal studies demonstrate the characteristic irritant properties of styrene on the upper respiratory tract.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to styrene.

No cardiovascular effects were observed in rats or mice exposed to concentrations as high as 1,000 ppm or 160 ppm, respectively, for 2 years (Cruzan et al. 1998, 2001).

Gastrointestinal Effects. Nausea was observed in humans exposed to 376 ppm styrene after 1 hour of exposure (Stewart et al. 1968). This effect is probably secondary to effects on the central nervous system, although mucociliary transport of styrene aerosol droplets from the upper respiratory tract to the gastrointestinal tract might also contribute to gastrointestinal irritation. A Russian study (Basirov 1975) reviewed by the World Health Organization (WHO 1983) investigated the effects of styrene on digestive function by testing the secretory, excretory, motor, and pepsinogen-generating functions of the stomach in 20 unexposed and 80 exposed workers. The authors reported that some workers in the styrene-butadiene synthetic rubber manufacture exposed to 60–130 mg/m^3 (14–31 ppm) styrene had decreased digestive function and decreased stomach acidity.

No histological alterations were observed in the stomach or intestines of rats exposed to 1,000 ppm (Cruzan et al. 1998) or mice exposed to 160 ppm (Cruzan et al. 2001) styrene for 2 years.

Hematological Effects. Several studies indicate that inhalation exposure of humans to styrene cause mild or no effects on the blood. In one study, the incidence of abnormal values for hematological parameters including erythrocyte, leukocyte, and platelet counts, and hemoglobin levels for 84 styrene workers generally exposed to <1 ppm styrene for 1–36 years was investigated. However, these workers were also exposed to intermittent high levels of styrene as well as to other chemicals. The percentages of the exposed group with abnormally low hemoglobin and erythrocyte values or abnormally high leukocyte values were less than those percentages in the 62-person control group. There were no abnormal

thrombocyte values reported in either the exposed or control groups (Thiess and Friedheim 1978). Findings from a group of 93 workers engaged in the manufacture of styrene polymers and exposed to generally <1 ppm styrene for 1–38 years were also presented in this study; only the incidence of abnormally low erythrocyte counts (in the group exposed to styrene) was found to be statistically significant ($p \leq 0.05$). However, because exposures could not be determined accurately and because there were concomitant exposures to other chemicals, the results of these studies are difficult to interpret.

Lowered erythrocyte counts, hemoglobin, platelets, and neutrophils and slightly higher mean corpuscular red cell volumes and neutrophil band counts were observed in workers in a styrene-butadiene rubber manufacturing plant (Checkoway and Williams 1982). The highest mean styrene level was 13.67 ppm. However, interpretation of this study is limited because multiple-chemical exposures were involved and exposure and clinical signs were measured at the same time and only once. An earlier study of styrene workers showed no definite pattern of hematological changes (Lorimer et al. 1978). In these studies, exposure levels were uncertain and multiple chemicals were involved.

In rats exposed to 49 ppm styrene, erythrocyte-aminolevulinate dehydratase (ALA-D) was depressed markedly. The decrease in enzyme activity was accompanied by a decrease in the enzyme content in bone marrow cells (Fujita et al. 1987). The investigators suggested that the changes may have been a result of styrene oxide reducing the enzyme protein is based on *in vitro* data. No hematological alterations were observed in 2-year studies in rats (Cruzan et al. 1998) and mice (Cruzan et al. 2001) exposed to concentrations as high as 1,000 or 160 ppm, respectively.

The well-conducted Thiess and Friedheim (1978) study as well as the more limited studies indicate that few adverse hematological effects occurred in styrene-exposed workers. However, the full meaning of the findings is not clear because of poor characterization of the exposure level and concurrent exposures to other chemicals.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to styrene.

No histological alterations were observed in skeletal muscle or bone of rats exposed to 1,000 ppm (Cruzan et al. 1998) or mice exposed to 160 ppm (Cruzan et al. 2001) for 2 years.

Hepatic Effects. Human studies on the hepatic effects of styrene inhalation frequently used serum levels of enzymes as indicators of liver dysfunction. In general, human studies have resulted in negative or equivocal results (Härkönen et al. 1984; Hotz et al. 1980; Lorimer et al. 1978; Thiess and Friedheim 1978). No significant alterations in alanine aminotransferase, aspartate aminotransferase, or γ-glutamyl transferase levels were observed in workers exposed to generally <1 ppm for 1–36 years (Thiess and Friedheim 1978) or 50–120 ppm for 5.1 years (Härkönen et al. 1984). A significant increase in γ-glutamyl transferase levels was observed in workers exposed to 5–20 ppm for up to 20 years; however, no alterations in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase levels were observed (Lorimer et al. 1978). Another study of workers (Hotz et al. 1980) found significant correlations between the exposure level (as measured by styrene metabolite concentrations in morning urine) and ornithine carbamoyl transferase, alanine aminotransferase, and γ-glutamyl transferase levels. Among workers exposed to 50–100 ppm, the increases in these enzymes were modest, 67.8, 55, and 64.9% of reference levels.

Animal studies provide evidence that the liver is a target tissue for styrene; however, the hepatotoxicity of styrene in mice is inversely related to the duration of exposure. Hepatic effects have been observed following acute- and intermediate-duration exposure, but not after chronic exposure and the severity of the effects decreases with continuing exposure. Exposure to 250 or 500 ppm for 1–4 days resulted in marked to severe hepatocellular necrosis and degeneration in mice (Morgan et al. 1993a, 1993b, 1993c). The necrosis was characterized as centrilobular coagulative necrosis and was accompanied by pooling of erythrocytes in dilated sinusoids (Morgan et al. 1993a). The necrosis was often observed after a single exposure to 500 ppm or a 2-day exposure to 250 ppm and the severity did not increase with increasing duration (Morgan et al. 1993a). However, continued exposure resulted in regeneration and repair of the initial hepatic damage. After 14 days of exposure, minimal to mild focal necrosis was observed in female mice exposed to 250 ppm and no hepatic effects were observed in male mice exposed to 250 ppm or male and female mice exposed to 500 ppm (Morgan et al. 1993a). Similarly, a 13-week exposure to 200 ppm resulted in focal loss of hepatocytes with siderosis and centrilobular aggregates of siderophages in female mice (Cruzan et al. 1997). No histological alterations were observed in the livers of mice exposed to 160 ppm for 2 years (Cruzan et al. 2001). Strain differences have also been detected in mice. Morgan et al. (1993c) found that B6C3F1 and C57BL/6 mice were more sensitive than DBA/2 mice, which were more sensitive than Swiss mice. The severity scores for hepatocellular degeneration/necrosis following a 4-day exposure to 250 ppm were 3.2–3.5 in B6C3F1 mice, 3.6 in C57BL/6 mice, 2.4–2.9 in DBA/2 mice, and 2.0 in Swiss mice.

Rats appear to be less sensitive than mice to styrene-induced hepatotoxicity. No histological alterations were observed in the livers of Sprague Dawley rats exposed to 1,000 ppm styrene for 13 weeks (Cruzan et al. 1997) or 2 years (Cruzan et al. 1998; Jersey et al. 1978). Parenchymal hydropic degeneration, steatosis, and congestion were observed in rats exposed to 300 ppm for 2 weeks (Vainio et al. 1979); the lack of incidence data limits the interpretation of these results.

Renal Effects. Based on the results of occupational exposure studies and animal toxicity studies, the kidney does not appear to be a sensitive target of styrene toxicity. Occupational exposure studies of workers exposed to 24 ppm (Viau et al. 1987), 53 ppm (Vyskocil et al. 1989), or 26 ppm styrene (Verplanke and Herber 1998) did not find significant alterations in urinary levels of β-microglobulin (not examined in Verplanke and Herber 1998 study), retinol-binding protein, or albumin. The Vyskocil et al. (1989) study also found no significant alterations in total protein, glucose, lysozyme, lactate dehydrogenase, or β-N-acetyl-D-glucosaminidase levels and Verplanke and Herber (1998) did not find alterations in β-galactosidase, N-acetyl-β-D-glucosaminidase, or alanine aminopeptidase. No histological alterations were observed in the kidneys following acute exposure of rats to 300 ppm (Vainio et al. 1979) or mice to 500 ppm (Morgan et al. 1993a), intermediate exposure of rats to 133–1,500 ppm (Cruzan et al. 1997; Spencer et al. 1942; Viau et al. 1987), or chronic exposure of rats to 1,000 ppm (Cruzan et al. 1998) or mice to 160 ppm (Cruzan et al. 2001). Additionally, no alterations in urinary levels of N-acetyl-D-glucosaminidase, γ-glutamyl transpeptidase, protein, or urea were observed in rats exposed to 500 ppm for 4 weeks (Loquet et al. 2000).

Endocrine Effects. Several occupational studies have examined potential endocrine effects in reinforced plastics industry workers exposed to styrene. Significant increases in serum prolactin levels were observed in male and female workers (Bergamaschi et al. 1996, 1997; Luderer et al. 2004; Mutti et al. 1984b). The serum prolactin levels significantly correlated with urinary metabolite (mandelic acid plus phenylglyoxylic acid) levels (Mutti et al. 1984b) and blood styrene levels (Luderer et al. 2004). Based on a logistic regression model, Luderer et al. (2004) estimated that workers exposed to styrene exposures >20 ppm would be more likely to have elevated serum prolactin levels than workers exposed to lower levels; a 10-fold increase in blood styrene concentrations would result in a 2.06-fold increase in serum prolactin levels. Similarly, Arfini et al. (1987) found that female styrene workers had an abnormal response to an intravenous dose of thyrotropin-releasing hormone; the levels of serum prolactin were significantly higher following exposure to thyrotropin-releasing hormone, as compared to referents. Two of these workers were re-examined after a 3-month period without styrene exposure; the serum prolactin response following thyrotrophin-releasing hormone exposure was similar to that in the referent group. No

significant alterations in the levels of thyroid stimulating hormone, follicle stimulating hormone, or luteinizing hormone were found in this study (Arfini et al. 1987). However, thyroid stimulating hormone levels were significantly correlated with urinary metabolite (mandelic acid plus phenylglyoxylic acid) levels. As noted in an editorial comment to this paper, the baseline levels of prolactin in the styrene workers were within the normal range and a supraphysiological dose of thyrotropin-releasing hormone level was used.

Significant increases in serum prolactin levels have also been observed in female rats exposed to 150 ppm, 8 hours/day for 10 days (Umemura et al. 2005). No significant alterations in serum prolactin levels were observed in similarly exposed male rats (Umemura et al. 2005) or in male rats exposed to approximately 150, 500, or 1,500 ppm 6 hours/day for 5 days (Jarry et al. 2002). Acute exposure to styrene did not result in significant alterations in thyroid stimulating hormone levels in male or female rats (Umemura et al. 2005).

Ocular Effects. Eye irritation in humans has been reported at high styrene concentrations (Carpenter et al. 1944; Stewart et al. 1968). Immediate eye irritation was reported in two human subjects exposed to 800 ppm styrene for 4 hours (Carpenter et al. 1944). Eye irritation was also noted by Stewart et al. (1968) in two of five volunteers exposed to 376 ppm styrene for 1 hour. Also, 345 styrene-exposed workers 98% male) were evaluated for ocular toxicity due to exposure to styrene (5–200 ppm) for 7–20 years. No evidence of optic neuritis, central retinal vein occlusion, or retrobulbar neuritis was found. Conjunctival irritation was a complaint of 22% of the 345 workers exposed to styrene levels above 50 ppm (Kohn 1978).

Eye and nasal irritation was observed in rats and guinea pigs exposed to 1,300 or 2,000 ppm styrene, 7–8 hours/day, 5 days/week for durations ranging from 21 to 30 weeks (Wolf et al. 1956). Rabbits and monkeys were exposed for up to 360 days with no effects.

3.2.1.3 Immunological and Lymphoreticular Effects

Two occupational studies have found significant alterations in lymphocyte subsets in styrene workers. Increase in percentage of CD4+/CD3CD4 T-lymphocytes and decrease in CD35+CD+ peripheral lymphocytes were observed in oil industry workers exposed to styrene, as compared to unexposed controls (Biró et al. 2002). However, these results should be interpreted cautiously because there were marked differences in smoking habits between the styrene workers and controls (80% styrene workers

smoked compared to 20% of controls) and the two groups were not matched for gender. Bergamaschi et al. (1995b) found an altered distribution of lymphocyte subsets in styrene workers exposed to an 8-hour time-weighted average (TWA) of 10–50 ppm. Some of these alterations, particularly the reduction in total T-lymphocytes (CD3+) and T-helper cells (CD4+), may be indicative of reduced cell-mediated immunity. This is supported by the finding of an impaired response to concanavalin in styrene workers exposed to a median styrene concentration of 26 ppm (Tulinska et al. 2000), 187–256 ppm (Somorovská et al. 1999) or 54–56 ppm (Somorovská et al. 1999). No alterations in the response to pokeweed mitogen were observed (Somorovská et al. 1999; Tulinska et al. 2000).

In patch-testing studies of cross-reactors to styrene, styrene 7,8-oxide was more sensitizing than styrene itself (Sjöborg et al. 1984). The authors interpreted this as evidence that styrene requires metabolism by skin aryl hydrocarbon hydroxylase to styrene epoxide for its sensitizing activity.

In animals, styrene exacerbated the inflammatory reaction in mice challenged with ovalbumin (Ban et al. 2006). Styrene-only exposure resulted in slight increases in Th2 cytokine (IL-4, IL-5, IL-13) and Th1 cytokine (interferon-γ) levels; however, the statistical significance of these alterations were not reported.

3.2.1.4 Neurological Effects

The available human data suggest that the nervous system is the most sensitive target following chronic-duration inhalation exposure. It is likely the most sensitive target following shorter-term durations, but this has not been as extensively investigated. In studies examining the acute neurotoxicity of styrene, impairment of the vestibular-oculomotor system was observed in experimental subjects exposed to 87 ppm for 1 hour (Ödkvist et al. 1982) or 376 ppm for 1 hour (Stewart et al. 1968). No alterations in the performance of balance tests were observed at 216 ppm for 1 hour (Stewart et al. 1968), 117 ppm for 2 hours (Stewart et al. 1968), or 99 ppm for 7 hours (Stewart et al. 1968). Although these NOAELs are higher than the LOAEL identified in the Ödkvist et al. (1982) study, the studies are not comparable. The Ödkvist et al. (1982) study used sensitive tests of vestibular-oculomotor function compared to the modified Romberg test (subjects stand on one foot with eyes closed, walk heel to toe, touch finger to nose) used in the Stewart et al. (1968) studies. An increase in the reporting of "feeling inebriated" was found in subjects exposed to 376 ppm for 1 hour (Stewart et al. 1968); no increases in subjective symptoms were observed in subjects exposed to 20 ppm for 3–4 hours (Seeber et al. 2004), 49 ppm for 6 hours with or without four 15-minute peak exposures to 98 ppm (Ska et al. 2003), or 216 ppm for 1 hour (Stewart et al. 1968). No alterations in reaction time were observed in subjects exposed to 20 ppm

for 3 or 4 hours (Seeber et al. 2004), 49 ppm for 6 hours with or without four 15-minute peak exposures to 98 ppm (Ska et al. 2003). Additionally, no alterations in color vision, olfactory threshold, or tests of memory or attention were observed in subjects exposed to 49 ppm for 6 hours with or without four 15-minute peak exposures to 98 ppm (Ska et al. 2003). No human studies examined neurotoxicity following intermediate-duration exposure.

In an international cohort of styrene workers, a significant association between mortality from central nervous system disease and cumulative styrene exposure was found (Welp et al. 1996c). The rate ratio was 3.29 (95% confidence interval [CI] of 0.48–22.65) for workers exposed to 25–49 ppm-years and 16.32 (95% CI 3.47–76.73) for those exposed for 200–349 ppm-years. A similar relationship was found for shorter durations of styrene exposure. The rate ratio was 2.33 (95% CI 0.40–13.56) for workers exposed for 6–11 months and 8.80 (95% CI 1.87–41.33) for workers exposed for 7–9 months. A significant association between mortality from epilepsy and duration of styrene exposure was found; the rate ratio in workers exposed for ≥10 years was 28.4 (95% CI 2.11–381.5). Time since first exposure was also significantly associated with mortality from epilepsy. Significant associations between mental disorders and duration of exposure and between suicide and duration of exposure were also found; however, for both of these causes of death, the rate ratio decreased with increasing duration of exposure and the investigators noted that lifestyle factors, rather than a direct effect of styrene, appear to be the most likely cause of the higher mortality.

A variety of neurological effects have been reported in workers chronically exposed to styrene including altered vestibular function, impaired hearing, decreased color discrimination, altered performance on neurobehavioral tests, and increased clinical symptoms. In general, these occupational exposure studies have several limitations. In most cases, the exposure levels reflect current exposure conditions and do not take into consideration past exposure to higher styrene levels that may have resulted in permanent damage. Some workers, particularly laminators, wore respiratory masks with or without canisters; many investigators estimated exposure based on biomarker levels, particularly urinary mandelic acid levels, while others did not. As discussed in greater detail in Sections 3.4.3, 3.4.3.1, and 3.8.1, urinary levels of styrene metabolites mandelic acid and phenylglyoxylic acid have been shown to correlate with time-weighted average styrene exposure levels and may be a more reliable biological indicator of styrene exposure in workplaces with highly variable styrene exposure levels. Significant differences between workers and referents were reported as LOAELs; however, the magnitude of the alteration may have been subclinical. A summary of the neurological effects observed in styrene workers is presented in Table 3-2.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Decreased color discrimination					
Chia et al. 1994	21	18.8 (range: 5–23)		6	Styrene exposure was estimated from mean urinary levels of MA (84.0 mg/g creatinine; range of 1.3–504.1 mg/g creatinine). Significant decreases in color discrimination, as expressed as total color difference score; no concentration-response relationship was found.
Kishi et al. 2001	21–42	6.2	4	10	Workers divided into three groups based on urinary MA levels. Significant differences in CCI, compared to age-matched controls, were found in the two highest groups. Mean CCI in 4, 10, and 46 ppm groups (CCI levels in age-paired controls): 1.21 (1.17), 1.23 (1.12), and 1.27 (1.13). Significant difference in CCI also found in analysis using 87 age-matched workers/ controls.
Gong et al. 2002	43	6.4		10	Workers divided into two groups based on combined urinary MA and PGA level dividing line of 0.24 g/g creatinine (approximately 10 ppm); both groups were significantly different from controls. Mean CCI (mean of right and left eyes) in controls, low exposure, and high exposure groups: 1.02, 1.09, and 1.14.
Gobba et al. 1991	41			16	Significant differences found when compared to age-matched controls (41 workers/controls) and in older workers (≥40 years of age). CCI was significantly different in workers exposed to ≥50 ppm compared to workers exposed to <50 ppm.
Triebig et al. 2001	19	4.5 (range: 1–21)		20	Significant increase in CCI in workers (mean of 1.29), compared to controls (mean of 1.10), when test conducted after work on a Thursday; no difference when measured before work on a Monday. Abnormal CCI values (>95th percentile age-dependent reference value) associated with urinary MA plus PGA levels of approximately 500 mg/g creatinine and higher.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Iregren et al. 2005	53–55	12.9–17.9 (range: 2–39)		22	Lifetime weighted average exposure calculated for each worker using historical exposure data. Total error score was significantly different from workers in the low exposure group (9 ppm).
Fallas et al. 1992	60	6.5 (range: >1–29)		24.3	Significant difference in the number of subjects with error axis in the red-green or blue-yellow ranges; no significant difference in calculated error scores.
Campagna et al. 1996	118	5.2 or 6.6		26	Mathematical threshold of impaired CCI was 4 ppm; the upper limit of the CI was 25.7 ppm.
Eguchi et al. 1995	57	7.0 (range: 0.2–26.8)	8	93	Significant difference in CCI between age-matched workers and controls. Workers divided into two groups—significant difference in CCI between high-concentration workers (urinary MA level of 1.06 g/L [range: 0.46–3.98 g/L] equivalent to 93 ppm) and age-matched controls. No difference in low concentration workers (urinary MA levels—mean of 0.02 g/L; range of 0.04–0.41 g/L; equivalent to 8 ppm). CCI scores in low and high exposure groups (CCI in age-matched controls) of 1.173 (1.118) and 1.332 (1.125).
Seeber et al. 2009b	242	Mean 5–8-6.4			Workers divided into three groups (low, medium, high) based on urinary MA and PGA levels. No significant differences in CCI score or visual contrast sensitivity were observed between groups. No associations were found when workers were divided into groups with long-duration-high exposure (air concentration of 27 ppm for over 15 years) and short duration-low exposure. Interpretation of these results is limited by the lack of a control group.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Reaction time					
Edling et al. 1993	20	9 (range: 1–25)	8.6		Simple and choice reaction time (measured before and after work).
Tsai and Chen 1996	45	8.3		21.9	Directly exposed workers compared to workers without direct styrene exposure (range of styrene levels was 0–6.4 ppm). Complex reaction time (continuous performance test): 532.8 and 495.6 ms in directly and indirectly exposed groups.
Jegaden et al. 1993	30	5		22.68	Reaction times (measured in morning before work) in workers and controls were 0.29 and 0.27 seconds for simple reaction time and 0.37 and 0.32 seconds for complex reaction time.
Fallas et al. 1992	60	6.5 (range: >1–29)	24.3		No significant difference in simple reaction time (23.7 seconds versus 22.7 seconds in controls).
Mutti et al. 1984a	50			25	Workers divided into four groups based on combined levels of urinary MA and PGA of <150, 150–299, 300–350, and >450 mmole/mole creatinine; 150 mmole/mole creatinine equivalent to 25 ppm. Complex reaction time in all workers and controls: 623.6 and 488.3 ms; the percent variations from matched controls were 120 and 165% in the 25 and 50 ppm groups.
Gamberale et al. 1976	106	2.7 (range: 0.1–11)		47	Mean styrene levels in each location were 16.6, 59.3, 41.6, and 101.4 ppm for resin appliers and 13.6 and 49.3 ppm for assemblers. The average styrene level for the six sites was 47 ppm. Simple reaction times (measured in morning before work) were 274 ms in workers and 260 ms in controls.
Cherry et al. 1980	27	NR		92	Simple reaction times (measured in morning before work) were 252 and 230 ms in workers and controls. A slower reaction time was also observed during the workshift.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Seeber et al. 2009a	213	Mean: 5–8-6.4			Workers divided into three groups (low, medium, high) based on urinary MA and PGA levels. No significant differences in choice reaction time were observed between groups. No association were found when workers were divided into groups with long-duration-high exposure (air concentration of 27 ppm for over 15 years) and short duration-low exposure. Interpretation of these results is limited by the lack of a control group.
Other neurobehavioral tests					
Chia et al. 1994	21	18.8 (range: 5–23)		6	Styrene exposure was estimated from mean urinary levels of MA (84.0 mg/g creatinine; range of 1.3–504.1 mg/g creatinine). Several tests of memory—Benton Visual Retention test (score 6.0 in workers vs. 7.7 in controls), digit symbol test (26.3 in workers vs. 38.0 in controls), and digit span (11.7 in workers vs. 15.6 in controls) were significantly affected. No significant relations between test score and urinary MA or PGA levels. No alteration in Santa Ana dexterity test or pursuit aiming.
Edling et al. 1993	20	9 (range: 1–25)	8.6		No effect on performance of symbol digit test.
Sato et al. 2009	67	Mean: 6.4 (range:0.08–10.3)		15.9	Significant increase in vibration perception threshold in upper and lower limbs in workers (mean urinary MA plus PGA level of 0.42 g/g creatinine equivalent to 16.9 ppm styrene in air). Increased vibration perception threshold in lower limbs in workers with mean past maximum urinary MA level of 0.30 g/g creatinine (equivalent to 15.9 ppm)
Jegaden et al. 1993	30	5		22.68	Significant impairment in performance on digit span test.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Fallas et al. 1992	60	6.5 (range: >1–29)		24.3	Significant alteration in aiming test. No significant alteration in Santa Ana test of dexterity, digit span, digit symbol, or Benton visual retention tests. However, there were significantly more workers with digit span test scores differing by more than one standard deviation from the mean, particularly in workers exposed to styrene for >10 years.
Mutti et al. 1984a	50			25	Workers divided into four groups based on combined levels of urinary MA and PGA of <150, 150–299, 300–350, and >450 mmole/mole creatinine; 150 mmole/mole creatinine equivalent to 25 ppm. Impaired performance on verbal learning test; no significant relationship with test scores in duration of exposure or exposure level.
Clinical symptoms					
Flodin et al. 1989	8 or 9	11.6 (range: 6–21)		6	High prevalence of clinical symptoms—abnormal tiredness (7/8 subjects) and short memory (8/8 subjects) in workers exposed to 6 ppm styrene; high prevalences of problems concentrating (7/9 subjects) and irritation (8/9 subjects) were also observed in workers exposed to 12 ppm. Prevalence was not compared to a referent group.
Edling et al. 1993	20	9 (range: 1–25)		8.6	Reported more acute symptoms than controls (mean of 2.9 in workers versus 1.8 in controls). More frequently responded positively to the following questions: are you abnormally tired, do you often have painful tingling in some parts of your body, do you have a headache at least once a week.
Checkoway et al. 1992	16–27	3.4–4.1	10.8	18.9	Higher prevalence of headache, dizziness, light headedness, fatigue, irritability, feeling "drunk" at work, and memory loss.
Cherry et al. 1980	27	NR		92	At the end of the workshift, changes in self-reported physical and mental tiredness and general health scores were correlated with blood styrene concentrations.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Hearing					
Triebig et al. 2009	17	14.6 (range: 10–26)		50	Average exposure was 30–50 ppm; in the past, workers were exposed to 80–100 ppm. Workers exposed to >85 dBA noise were excluded from analysis. Lower hearing thresholds were observed at 1,000–1,500 and 8,000–12,500 Hz. Significant improvement in hearing following an exposure-free period.
Triebig et al. 2009	31	6.3 (range: 1–26)	40		No significant alterations in hearing threshold among workers with urinary MA plus PGA levels of 970 mg/g creatinine (approximately 40 ppm).
Morata et al. 2002	65	17 (range: 1–39)		3.68	Noise level 82 dBA. A higher prevalence of high frequency hearing loss (47%) compared to controls (33%), but difference was not statistically significant. Significantly poorer thresholds were observed at 2, 3, 4, 6, and 8 kHz in the styrene group. The OR of 1.19 (95% CI, 1.11–1.28) times greater for each 1 year of age was calculated and 2.44 times greater (95% CI, 1.01–5.89) for each increment of 1 mmol MA/g creatinine in urine.
Śliwińska-Kowalska et al. 2003	194	NR		15.6	Current styrene concentrations ranged from 0.05 to 46 ppm; average worklife mean styrene concentration was 15.6 ppm. Average noise level was 80.3 dBA. Abnormal audiograms were found in 63.3% of styrene workers, compared to 33.8% in the unexposed controls. The OR of hearing loss was 5.2 (95% CI, 2.9–8.9). A positive linear relationship between styrene working life exposure levels and hearing thresholds.
Morioka et al. 1999	93	9.4		16	Sound levels in the workplace ranged from 53 to 95 dBA. Significant correlation between individual percentiles of the upper limit of hearing and styrene concentrations in workers exposed for ≥5 years; the prevalence rates below the 75th percentile were significantly higher than 25% in workers exposed to >16 ppm.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Möller et al. 1990	18	10.8 (range: 6–15)	18		No styrene-related alterations in the pure-tone audiometry and speech discrimination tests were found. Seven workers displayed abnormal results in distorted speech and/or cortical response audiometry tests.
Calabrese et al. 1996	20	7.6 (range: 2–23)	36		All workers had normal hearing thresholds and no abnormalities of stapedial reflex were found. No significant effect on ABRs (as compared to 10 control subjects) were observed; additionally, when nine subjects were re-tested after 3 weeks without exposure, no significant difference between pre- and postrecovery values were found.
Vestibular					
Möller et al. 1990	18	10.8 (range: 6–15)		18	Significantly higher sway with eyes open or closed in the static posturography test, increased latency in saccade test, a phase lag and depressed gain in unpredictable and predictable stimulation in the smooth eye pursuit test, and impaired ability to suppress vestibulo-ocular reflex in sinusoidal and pseudorandomized tests.
Toppila et al. 2006	88	NR		24.8	Nonlaminators used as the comparison group; 88 pairs of age-matched workers were used for postural stability tests; the mean styrene and MA PGA concentrations for these pairs were 24.8 ppm and 1.4 mmol/L for the laminators and 4.8 ppm and 0.3 mmol/L for the nonlaminators. Poorer performance in dynamic tests on the static platform. In the tilting platform and virtual reality tests, sway velocity was greater and workers became unstable and displayed large correctional movements.
Calabrese et al. 1996	20	7.6 (range: 2–23)		36	Abnormal results in the vestibulo-ocular tests, these alterations persisted after the 3-week recovery period. No alterations in visual suppression test or postural performance were found.

Table 3-2. Summary of Occupational Exposure Studies Examining Neurological End Points

Reference	Number of workers	Mean duration of exposure (years)	NOAEL (ppm)	LOAEL (ppm)	Comments
Nerve conduction velocity					
Seppäläinen and Härkönen 1976	96	5	30		Styrene exposure was estimated using end-of-shift urinary MA levels collected weekly for 5 consecutive weeks. No significant differences in median, ulnar, deep peroneal, or posterior tibial nerve motor or sensory conduction velocities were observed, as compared to a referent group with a similar age distribution.
Štětkářová et al. 1993	15	11		50	Decreased peripheral conduction velocities in median and tibial nerves were observed in female styrene workers; prolonged latencies of peripheral and cortical somatosensory evoked potentials were also observed in the female workers exposed to styrene.
Triebig et al. 1985	11	4	100		No significant alterations in maximum conduction velocity in the ulnar nerve or distal conduction velocity of the sensory fibers of the ulnar and median nerves.

ABR = auditory brainstem response; CCI = color confusion index; CI = confidence interval; LOAEL = lowest-observed-adverse-effect level; MA = mandelic acid; MS = millisecond; NOAEL = no-observed-adverse-effect level; NR = not reported; OR = odds ratio; PGA = phenylglyoxylic acid

Color vision appears to be one of the more sensitive targets of styrene toxicity, with many studies reporting alterations. Color vision was typically measured using the Lanthony desaturated panel D-15 test in which the subjects were asked to arrange 15 painted caps in a line with definite chromatic sequence; the color confusion index (CCI) quantifies the number of types of mistake. A significant correlation between CCI and urinary mandelic acid concentration (after correction for age) was observed in workers at fiberglass reinforced plastic facilities (Kishi et al. 2001). When workers were divided into three groups based on end-of-shift urinary mandelic acid levels, there were significant differences between CCI in workers with a mean a mandelic acid level of 0.14 or 0.65 g/L and age-matched referents; no difference was found for the third group with a mean mandelic acid level of 0.05 g/L. The investigators estimated that these urinary mandelic acid levels were equivalent to styrene exposure levels of 4, 10, and 46 ppm. Thus, this study identifies a NOAEL of 4 ppm and a LOAEL of 10 ppm for decreased color discrimination. Similarly, Gong et al. (2002) found significantly higher CCI values in workers at a fiberglass reinforced plastic boat facility with end-of-shift urinary mandelic acid and phenylglyoxylic acid levels of ≥0.24 g/g creatinine or <0.24 g/g creatinine; a mandelic acid plus phenylglyoxylic acid urine level of 0.24 g/g creatinine is equivalent to a styrene exposure level of 10 ppm. A significant increase in CCI was also observed in workers at fiberglass reinforced plastic facilities as compared to age-matched controls (Gobba et al. 1991); although the mean styrene concentration was 16 ppm for all workers (n=73), the mean for the subset of workers used for age-matched analysis was not reported. When workers were stratified based on styrene air levels, workers exposed to 49 ppm styrene had significantly higher CCI scores than workers exposed to lower levels. In contrast to other studies, Gobba et al. (1991) did not find a significant relationship between end-of-shift urinary mandelic acid levels and CCI; however, urinary styrene levels correlated with CCI values. CCI values were significantly higher in laminators at a boat manufacturing facility with a median urinary mandelic acid plus phenylglyoxylic acid levels of 472 mg/g creatinine compared to control subjects when the test was administered on a Thursday after work (Triebig et al. 2001). Although CCI values were also elevated on a Monday before work, the values were not significantly different from controls. Classifying CCI values for the workers as normal or abnormal (exceeding the 95th percentile of the age reference values) demonstrated that abnormal CCI values were typically associated with urinary mandelic acid plus phenylglyoxylic acid levels of approximately 500 mg/g creatinine and higher (approximately 20 ppm styrene in air for 8 hours). Significantly higher CCI values were observed in fiberglass reinforced workers with a mean urinary mandelic acid levels of 1.06 g/L, which is roughly equivalent to a styrene exposure level of 93 ppm (Eguchi et al. 1995). This study did not find significant alteration in workers with a mean urinary mandelic acid level of 0.02 g/L, equivalent to 8 ppm. Another study of fiberglass reinforced plastic workers (some of this cohort was examined by Gobba et al. 1991 and Campagna et al.

1995) found a significant association between CCI and styrene exposure levels (Campagna et al. 1996). The investigators concluded that color vision impairment could be detected at styrene levels of 4 ppm with a 95% upper confidence limit of 26 ppm. Two other occupational exposure studies using different measures of color vision impairment also found significant alterations. Chia et al. (1994) found significantly poorer color discrimination, after adjusting for age, education, and alcohol consumption, in 21 workers at a fiber-reinforced plastic boat manufacturing facility; the styrene exposure level of 6 ppm was estimated from a mean end-of-shift urinary mandelic acid level of 84.0 mg/g creatinine. No relationship between the total color difference score and the urinary mandelic acid level was found. In 60 workers in the shipbuilding industry with a mean styrene exposure level of 24.3 ppm, a significantly higher incidence of workers with errors in the blue-yellow or red-green ranges, compared to a referent group, was found (Fallas et al. 1992). Total error score was significantly different in workers, with a lifetime weighted average exposure level of 22 ppm styrene, as compared to workers in a low exposure group (9 ppm) (Iregren et al. 2005). In contrast to these results, Seeber et al. (2009b) found no significant association between CCI scores or visual contrast sensitivity among styrene workers with long-term exposure to average styrene concentrations up to 27 ppm; identification of a NOAEL from this study is limited by the lack of a control group.

Several studies found improvements in color vision following an extended period of no styrene exposure or lower exposure. Triebig et al. (2001) reported a significant improvement in CCI scores following a 4-week period with no styrene exposure; in contrast, no improvement in CCI scores was found in another group of styrene workers following a 1-month period without styrene exposure (Gobba et al. 1991). Two studies found significant improvements in color vision (age-adjusted color confusion score or CCI score) were observed in styrene workers following a decrease in styrene air level (Castillo et al. 2001; Triebig et al. 2001). However, one study found no change in age-adjusted near visual contrast sensitivity following a decrease in styrene exposure levels (Castillo et al. 2001).

A number of studies have found significant alterations in performance on a variety of neurobehavioral tests; among these studies, reaction time appears to be the most frequently examined end point. Significant increases in simple reaction time have been observed in styrene workers exposed to concentrations of 21.9, 22.68, 47, or 92 ppm (Cherry et al. 1980; Gamberale et al. 1976; Jegaden et al. 1993; Tsai and Chen 1996); tests for reaction time were measured in the morning before the work shift, suggesting that the effect was not due to acute exposure to styrene. The reaction times were 4–10% slower in the styrene workers as compared to the referent groups. No significant alterations in simple reaction time were observed in workers exposed to 8.6 ppm (Edling et al. 1993) or 24.3 ppm (Fallas et al.

1992). Similarly, complex reaction time was significantly increased among styrene workers exposed to 21.9, 22.68, or 25 ppm (Fallas et al. 1992; Jegaden et al. 1993; Mutti et al. 1984a); the variance from controls ranged from 7.5 to 20%. No alterations in complex reaction time were observed in workers exposed to 8.6 ppm (Edling et al. 1993). No alterations in choice reaction time were observed in styrene workers exposed up to 27 ppm averaged over 15 years (Seeber et al. 2009a); this value was not identified as a NOAEL because the study did not include a control group. Impaired performance on the digit span test, which measures attention/concentration, was observed in workers exposed to 6 ppm (Chia et al. 1994), 22.68 ppm (Jegaden et al. 1993), or 24.3 ppm (Fallas et al. 1992). Other neurobehavioral performance tests that may be altered by chronic exposure to styrene included digit symbol or symbol digit tests at 6 ppm (Chia et al. 1994), vibration perception threshold at 15.9 ppm (Sato et al. 2009), memory at 25 ppm (Mutti et al. 1984a), and visuomotor at 50 ppm (Mutti et al. 1984a) or 75 ppm (Lindstrom et al. 1976). However, other studies have not found significant alterations in digit symbol at 8.6 ppm (Edling et al. 1993), 24.3 ppm (Fallas et al. 1992), or 25 ppm (Mutti et al. 1984a), or memory at 75 ppm (Lindstrom et al. 1976). By pooling response data for several tests of neurobehavioral performance, Mutti et al. (1984a) were able to analyze exposure-response relationships. When workers were divided into four groups based on morning urinary mandelic acid and phenylglyoxylic acid levels, the number of subjects with abnormal scores on greater than one, two, or three tests increased with increasing exposure concentration. Additional analyses demonstrated that the exposure intensity and duration of exposure affected a worker's performance on neurobehavioral tests and the duration of exposure appeared to affect performance more than exposure intensity.

Clinical symptoms of neurotoxicity have been reported by styrene workers; commonly reported symptoms included headaches, dizziness, impaired memory, and feeling "drunk". At 6 or 12 ppm, abnormal tiredness and short memory were reported by most of the styrene workers examined by Flodin et al. (1989); problems concentrating and irritation were also reported by most workers exposed to 12 ppm. After a 7-month period without styrene exposure, there was a marked improvement in symptoms and the mean number of symptoms reported was 1.9, compared to 5.3 reported 7 months earlier. Fiberglass reinforced plastic industry workers exposed to 18.9 or 50.0 ppm reported a higher prevalence of headaches, dizziness, light headedness, fatigue, irritability, feeling "drunk", and memory loss (Checkoway et al. 1992); the prevalence of clinical signs was not significantly increased in workers exposed to 10.8 ppm. Increases in the incidence of headache, memory disturbances, forgetfulness, dizziness, and sensory symptoms in the upper and lower extremities were observed in workers with high exposure to styrene compared to those with low styrene exposure (Matikainen et al. 1993a); exposure levels were not reported. A significantly higher incidence of subjective symptoms (nausea, feeling of

drunkenness, dizziness, and disturbance) was observed in styrene workers exposed to 4–164 ppm, as compared to controls (Geuskens et al. 1992). No significant difference in the incidence of symptoms related to cognitive motor disturbances (lack of concentration, understanding, trouble with movements) was found. Fiberglass boat manufacturing workers exposed to 92 ppm reported a higher prevalence of physical and mental tiredness at the end of the work shift than controls (Cherry et al. 1980). No alterations in the reporting of clinical symptoms were observed in plastic industry workers exposed to a mean concentration of 8.6 ppm (Edling et al. 1993).

Styrene-induced damage to hearing and the vestibular system have been examined in a number of studies of chronically exposed workers. Several studies have reported significant associations between styrene exposure and hearing impairment; however, interpretation of the findings of most of these studies is limited by confounding exposure to noise or other solvents. Noise studies have found that exposure to >85 dB for over 10 years can result in a 10% hearing loss (Prince et al. 1997). Triebig et al. (2009) did not find an association between hearing loss and current styrene exposure among workers at a boat building plant (workers exposed to noise levels >85 dBA were excluded from the analysis); the high exposure group had a mean urinary mandelic acid plus phenylglyoxylic acid level of 970 mg/g creatinine (approximately 40 ppm). However, among long-term workers (exposed to styrene for >10 years) exposed to high levels of styrene, several effects were observed including hearing losses at 1,000–1,500 and 8,000–12,500 Hz and an improvement in hearing function following a non-exposure period; the average exposure level was 30–50 ppm with >50 ppm exposure (80–100 ppm) in the past. Morioka et al. (1999) found an increased prevalence of workers with a urinary mandelic acid level of >0.3 g/L (approximately 16 ppm) with an upper frequency of hearing below the 75th percentile for normal. However, interpretation of the results is limited by confounding exposure to noise and exposure to other solvents, particularly toluene, which has been shown to be ototoxic. The noise levels ranged from 53.0 to 95.0 dBA with 14% of the measurements exceeding 85 dBA. Another study (Muijser et al. 1988) of styrene workers found a significant difference in hearing threshold at 8 kHz between indirectly exposed workers (mean styrene level of 14 ppm) and directly exposed workers (mean styrene level of 32 ppm); however, no differences were found in comparisons of indirectly and directly exposed workers with referent workers. The noise level for both groups of styrene workers was 80–85 dBA for most of the day. Śliwińska-Kowalska et al. (2003) found a significantly elevated risks of hearing loss among styrene workers exposed to a mean styrene concentration of 15.6 ppm (average noise level of 80.3 dBA). The odds ratio (adjusted for noise and gender) in workers only exposed to styrene was 5.2 (95% CI 2.9–8.9). The hearing losses were found within the range of 2–8 kHz. Morata et al. (2002) found significant decreases in hearing thresholds at 2, 3, 4, and 6 kHz in workers exposed to 0.05–22 ppm (mean of

4 ppm); no difference in the prevalence of high frequency hearing loss, as compared to referent workers, was found. The fairly wide range of exposure levels adds a great deal of uncertainty to estimating the LOAEL from this study; although the mean exposure is reported as the LOAEL in Figure 3-1, this value may be an overly conservative estimate of the true LOAEL. Other studies have not found significant alterations in hearing. Möller et al. (1990) found no indications of hearing loss in workers exposed to 18 ppm styrene. Sass-Korstak et al. (1995) did not find significant relationships between lifetime styrene exposure and hearing loss in workers at fiber-reinforced plastics manufacturing facilities. The cumulative styrene exposure level was calculated using data for current exposure (25 ppm for directly exposed workers and 8 ppm for indirectly exposed workers), length of time in each job category, and a downward adjustment for self-reported respirator use. The average noise levels (L_{eq}) were 88.1 and 89.2 dBA for the directly and indirectly exposed workers, for nonexposed workers, a sound level of 80 dBA was assumed. In another study of fiberglass workers (Calabrese et al. 1996), no significant alterations in audiometric tests or auditory brainstem response were observed in workers exposed to a mean styrene level of 36 ppm. Additionally, a 3-week recovery period did not result in any significant changes in auditory brainstem responses (pre- and post-recovery) in nine of the workers.

Other studies have examined workers for styrene-induced vestibular effects. Significant alteration in tests of central vestibulo-ocular and opto-ocular motor movements (i.e., static posturography, smooth eye pursuit, saccade, and vestibulo-ocular reflex tests) were observed in workers at a plastic boat manufacturing facility exposed to a TWA styrene concentration of 18 ppm (Möller et al. 1990). No indications of labyrinthine or peripheral vestibular lesions were observed. Toppila et al. (2006) also found significant alterations in postural stability in workers at fiberglass-reinforced plastic boat manufacturing facilities exposed to 25 ppm styrene. In contrast, Calabrese et al. (1996) did not find significant alterations in visual suppression tests or postural stability in fiberglass plant workers exposed to 36 ppm styrene. Significant alterations in vestibulo-ocular reflex were found. A 3-week recovery period did not result in significant changes in the test results.

Styrene's potential to impair odor threshold and vibration potential threshold have also been examined in styrene workers. Two studies examined styrene's potential to affect olfactory function. No alterations in three clinical tests of olfactory function were observed in styrene workers exposed to 24.6 ppm styrene for minimum of 4 years (Dalton et al. 2003). Another study by these investigators (Dalton et al. 2007) found a significant impairment in performance on an odor identification test between styrene workers (current exposure levels ranging from 11 to 22 ppm as assessed via urinary mandelic acid plus phenylglyoxylic acid levels) compared to non-exposed workers (current styrene levels of 0.6–7.1 ppm).

However, no significant relationships between current (on the day of olfactory testing or on the preceding day) or historical styrene exposure levels were found, suggesting that the difference was not related to styrene exposure. Sato et al. (2009) reported significant differences in vibration potential threshold in upper and lower limbs in workers at fiberglass-reinforced plastic boat facilities with a mean urinary mandelic acid plus phenylglyoxylic acid level of 0.42 g/g creatinine (approximately 17 ppm styrene in air), as compared to age-matched controls; however, the relationship between current urinary metabolites level and vibration threshold potential was not statistically significant. A past maximum urinary mandelic acid level of ≥50 ppm were significantly associated with impaired vibration threshold potential.

Workers exposed to styrene in several industries at mean concentrations of 5–125 ppm had mild sensory neuropathy characterized by decreased sensory conduction amplitude and increased duration, but there were too few people to define a NOAEL (Rosen et al. 1978). Peripheral neuropathy and reduced nerve conduction velocity was also reported in an individual following a 2-day exposure to an unknown amount of styrene (and other chemicals) (Fung and Clark 1999). Leg weakness, leg muscle cramps, and paresthesia were also reported in two styrene workers (Gobba et al. 1995). Moderate sensorimotor neuropathy of the demyelinating type was diagnosed in both cases based on the clinical symptoms and the decreased motor nerve conduction velocity in the peroneal nerve and decreased sensory nerve conduction velocity in the sural and median nerves. Alterations in nerve conduction velocity have also been observed in styrene workers. Decreased peripheral conduction velocities in the median and tibial nerves and prolonged latencies of peripheral and cortical somatosensory evoked potentials were observed in female styrene workers exposed to 30–130 ppm (midpoint of the range is 50 ppm) (Štětkářová et al. 1993). Significant decreases in ulnar and peroneal maximum conduction velocities and increased peroneal motor distal latencies were observed in fiber reinforced workers exposed with urinary mandelic acid levels (end of shift) of ≥250 mg/L, as compared to referent workers. Motor distal latencies in the workers with urinary mandelic acid levels ≥250 mg/L were also significantly lower than in workers with urinary mandelic acid levels <250 mg/L (Yuasa et al. 1996). In contrast, no alterations in motor or sensory nerve conduction velocity in the ulnar, median, deep peroneal, or posterior tibial nerve were observed in workers exposed a to TWA styrene concentration of 30 ppm (based on urinary mandelic acid excretion) (Seppäläinen and Härkönen 1976), and no alteration in motor or sensory nerve conduction velocity was observed in workers exposed to approximately 100 ppm for a median of 4 years (Triebig et al. 1985). Although Seppäläinen and Härkönen (1976) did not find alterations in nerve conduction velocity, they found abnormal EEGs in 24% of the styrene workers, as compared to reported values for the normal population. The mean urinary mandelic acid level (975 mg/dm^3) was higher in workers with abnormal EEGs compared to those with normal readings (750 mg/dm^3). Similarly, a significantly higher absolute

EEG power in alpha band in the fronto-temporal region of the brain was found in workers with high styrene exposures, as compared to workers with low-level exposure (Matikainen et al. 1993a).

The majority of the available animal neurotoxicity studies have focused on hearing impairment. Hearing loss and a loss of outer hair cells (OHC) in the organ of Corti were observed in rats acutely exposed to 1,000 ppm (Campo et al. 2001; Lataye et al. 2003) or 1,600 ppm (Crofton et al. 1994). In contrast, acute exposure of guinea pigs to 1,000 ppm did not result in hearing loss or OHC damage (Lataye et al. 2003). Intermediate-duration exposure studies have consistently found hearing loss and loss of OHC in rats exposed to ≥750 ppm styrene (Campo et al. 2001; Lataye et al. 2000, 2001; Loquet et al. 2000; Pouyatos et al. 2002; Pryor et al. 1987; Yano et al. 1992). Exposure to 600–650 ppm resulted in OHC losses but no alterations in hearing threshold (Loquet et al. 1999; Makitie et al. 2002; Pouyatos et al. 2002). A NOAEL of 300 ppm was identified by Makitie et al. (2002).

Other neurological effects that have been observed in animal studies include lethargy and unsteady gait in mice exposed to 250 ppm for 2 weeks (Cruzan et al. 1997), an increase in astroglial alterations at 320 ppm (Rosengren and Haglid 1989), a decrease in nerve conduction velocity in rats exposed to 2,000 ppm, but not 200 ppm, for 32 weeks (Yamamoto et al. 1997), and concentration-related alterations in nystagmus elicited by optokinetic, vestibular, simultaneous optokinetic-vestibular, and saccadic stimulation in rats exposed to 830–4,000 ppm styrene for at least 60 minutes (actual duration of exposure was not reported) (Niklasson et al. 1993).

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

Information on the reproductive effects of styrene in humans is available from epidemiological studies of the reproductive outcomes of females employed in the various industrial operations in which styrene is used. However, exposures to styrene were not adequately quantified in any of the studies cited. In one study, spontaneous abortions among 9,000 Finnish chemical workers from 1973 to 1976 were analyzed (Hemminki et al. 1980). The risk of spontaneous abortion expressed as number of abortions per 100 pregnancies) was significantly higher in women employed in styrene production compared to all women in Finland 15.0 vs. 5.5). However, this increase was not detected in a follow-up study of the same workers (Hemminki et al. 1984). An increase in the occurrence of spontaneous abortions was also

observed in a study of 76 women involved in processing polystyrene plastics (McDonald et al. 1988); the ratio of observed to expected abortions was 1.58 (95% CI 1.02–2.35). The possible embryotoxic effects of styrene on 67 female lamination workers compared to 67 age-matched controls were evaluated in a second study (Härkönen and Holmberg 1982). The number of births was significantly lower among the workers exposed to styrene. This result was explained in part by a greater number of induced abortions in the styrene-exposed group. The number of spontaneous abortions was not elevated in the exposed women. No increased risk of spontaneous abortions among workers processing polymerized plastics or heated plastics made of vinyl chloride or styrene was reported (Lindbohm et al. 1985). The authors reported that the statistical power of the study was low due to the small study population. These studies are not conclusive since the workers were exposed to chemicals other than styrene in the workplace and the concentrations of styrene were not adequately reported. Two studies have examined the potential of styrene to induce menstrual disturbances. A significant increase in the incidence of oligomenorrhea was observed in petrochemical industry workers; the adjusted odds ratio was 1.65 (95% CI 1.05–2.55) (Cho et al. 2001). Although the odds ratio includes an adjustment for exposure to other aromatic chemicals, there was potential for exposure to other chemicals; only three workers were exposed to styrene only and none of these women reported oligomenorrhea. In contrast, no significant alterations were observed in women working at reinforced plastics facilities with a mean styrene exposure level of 52 ppm for women directly exposed to styrene and 13 ppm for those indirectly exposed (Lemasters et al. 1985). Several studies have examined levels of prolactin, follicle stimulating hormone, and luteinizing hormone levels in female styrene workers; the results of these studies are discussed in Section 3.2.1.2, Endocrine Effects.

Several studies have also examined styrene's potential to induce male reproductive effects. A significant decrease in sperm concentration, total sperm count, percentage of normal sperm, and percentage of nonvital sperm and an increase in sperm velocity were observed in 23 workers employed at a styrene manufacturing facility for approximately 6 months, as compared to levels during the first week of employment (Kolstad et al. 1999a; results are also presented in Kolstad et al. 1999b). No significant relationships between urinary mandelic acid level and sperm density, total sperm count, or proportion of sperm with normal morphology were observed. A positive correlation between mandelic acid levels and the percentage of nonvital sperm was found, but the trend test was not statistically significant. In a large multinational study of male styrene workers, no significant alterations in time-to-pregnancy were found; the odds ratio, adjusted for maternal age, use of oral contraceptives, maternal and paternal smoking habits, time-to-pregnancy starting year, length of employment, and country, was 0.79 (95% CI 0.59–1.05) (Kolstad et al. 2000). Additionally, no significant alterations in fertility rates were found when workers were divided into groups based on length of exposure, period of attempting pregnancy, or exposure group

(monitoring data from a subset of facilities were used to divide workers into different exposure groups) (preliminary data from this study was reported by Kolstad et al. 1999c). Similarly, no significant alterations in time to pregnancy among styrene workers exposed to high or intermediate/low exposure levels (based on urinary mandelic acid levels) (Sallmén et al. 1998).

Two animal studies have examined the reproductive toxicity of styrene following inhalation exposure. No statistically significant alterations in the frequency of abnormal sperm heads were observed in mice 3–5 weeks after exposure to 300 ppm for 5 days (Salomaa et al. 1985). In a two-generation study in rats (Cruzan et al. 2005b), no significant alterations in reproductive performance, estrous cycle length, spermatogenic parameters, or histological alterations in reproductive tissues were observed at concentrations up to 500 ppm.

3.2.1.6 Developmental Effects

Limited information concerning developmental effects of styrene in humans is available from studies of delivery outcome of women employed in the plastics industry (processing styrene or polyurethane plastics). Case-control studies performed in Sweden and Norway did not detect an increase in the odds ratio for developmental effects (stillbirth, infant death, malformations, low birth weight) in women who worked in the plastic industry (Ahlborg et al. 1987). However, actual levels of styrene exposure were not known for either group of workers. Another study did not find significant increases in the occurrence of congenital malformations in children of men or women working at reinforced plastics facilities (Härkönen et al. 1984). A <4% lower birthweight were observed in the children of women who worked in the reinforced plastics industry in areas with elevated levels of styrene (mean concentration of approximately 82 ppm) during pregnancy (Lemasters et al. 1989). However, this decrease was not statistically significant ($p=0.08$). These studies suggest that developmental effects in exposed workers are not of major concern, but the data are not adequate to exclude this effect. Moreover, interpretation of the results is complicated due to exposure of the workers to other chemicals in the workplace such as toluene, xylene, acetone, methylene chloride, and methyl ketone (Lemasters et al. 1989), as well as thermal degradation products of styrene polymers (Ahlborg et al. 1987). Workers may also be exposed to aerosols containing aldehydes, ketones, alcohols, esters, acids, and anhydrides. An expert panel convened by the National Toxicology Program (NTP 2006) concluded that the human data are not sufficient to evaluate the potential developmental toxicity of styrene in humans.

The developmental toxicity of styrene has been examined in several animal studies. The average fetal crown-rump length was significantly reduced in rats exposed to 300 ppm on gestational days 6–15, but was not affected in rats exposed to 600 ppm (Murray et al. 1978); the investigators concluded that this effect was not treatment-related. A few skeletal variants such as lumbar spurs and delayed ossification of sternebrae occurred in the styrene-exposed litters at a higher incidence than the control litters; however, the occurrence of this effect was similar to historical controls. No developmental effects were observed in rabbits exposed to 600 ppm styrene on days 6–18 of gestation (Murray et al. 1978). Although there was a significant increase in the incidence of unossified sternebrae in the 600 ppm group, it did not exceed that found in historical control data. No significant alterations in the number of live fetuses, dead/resorbed fetuses, or malformed fetuses were observed in the offspring of mice exposed to 250 ppm styrene on days 6–16 of gestation (Kankaanpää et al. 1980). In the same study, exposure of hamsters to 1,000 ppm of styrene on days 6–18 of gestation resulted in a significant increase in the number of dead or resorbed fetuses; no other alterations were observed (Kankaanpää et al. 1980). No effects were observed at 750 ppm. Similarly, no developmental effects were observed in a two-generation study in which rats were exposed to 500 ppm prior to mating, during mating, and during gestation and lactation (Cruzan et al. 2005b). In contrast, Katakura et al. (1999, 2001) reported a significant increase in neonatal deaths in the offspring of rats exposed to 300 ppm on gestational days 6–20.

Two studies have examined potential neurodevelopmental effects. Some minor alterations in tests of developmental milestones (incisor eruption), functional observational battery tests (forelimb grip strength), and swimming maze test were observed in the F2 offspring of rats exposed to 500 ppm in a two-generation study; these alterations were attributed to a lower body weight rather than a neurodevelopmental effect of styrene (Cruzan et al. 2005a). No alterations in locomotor activity, acoustic startle response, or brain morphology and weights were observed in this study. Another study found delays in righting reflex and incisor eruption in the offspring of rats exposed to 300 ppm on gestational days 6–20 (Katakura et al. 2001). This study (Katakura et al. 1999, 2001) also found alterations in homovanillic acid levels in the cerebrum and 5-hydroxyindoleacetic acid levels in the hippocampus of the offspring in the 300 ppm group.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

A number of studies have examined the carcinogenic potential of styrene in workers at styrene manufacturing and polymerization facilities, reinforced plastics facilities, and styrene-butadiene manufacturing facilities and among community members exposed to elevated styrene workers. Although there are several epidemiologic studies which suggest there may be an association between styrene exposure and an increased risk of leukemia and lymphoma, the evidence is generally inconclusive due to multiple chemical exposures and inadequate documentation of the levels and durations of exposure to styrene.

Of the industries examined, workers employed at glass-reinforced plastics manufacturing facilities are likely to be exposed to higher levels of styrene and have lower potential for exposure to other carcinogenic agents. Some studies of glass-reinforced plastic workers have found suggestive evidence of increased cancer risks, particularly in workers with longer exposures to higher levels of styrene. No alterations in the number of deaths from cancer were observed in workers with high styrene exposure (mean levels at two facilities were 42.5 and 71.5 ppm) (Okun et al. 1985). In a follow-up study of these workers (Ruder et al. 2004), a significant increase in the number of deaths from urinary tract cancer (standardized mortality ratio [SMR] 3.44; 95% CI 1.26–7.50) was observed among workers with high styrene exposure; a trend for increasing SMRs for urinary tract cancer with increasing duration of exposure was also observed. The SMRs were not significantly elevated for other cancer types. In a very large epidemiological study of nearly 16,000 workers in the styrene plastic industry, the death rate from leukemia was twice as high in areas of high exposure as in areas of low exposure (Wong 1990); however, there were no statistically significant differences. In a follow-up study conducted 12 years later (Wong et al. 1994), significant increases in deaths from all cancers (SMR 115.5, 95% CI 104.8–127.1), cancer of the esophagus (SMR 191.7; 95% CI 104.8–321.7), bronchus, trachea, or lung (SMR 140.6; 95% CI 119.3–164.0), cervix or uteri (SMR 283.5; 95% CI 135.9–521.3), and female genital organs (SMR 201.6; 95% CI 107.4–344.8) were observed. However, no relationships between styrene exposure (exposure level or duration of exposure) and deaths from these cancer types were found. No significant increases in the incidence of non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, leukemia, or all lymphohematopoietic malignancies were observed in workers at Danish reinforced plastics facilities in which 50–100% of the workers were involved in reinforced plastics production (Kolstad et al. 1993, 1994). However, when workers were divided by first year of employment, there was a significant increase in leukemia (standard incidence ratio [SIR] 1.69, 95% CI 1.09–2.49) among workers with a latency of ≥10 years and first year of employment of 1964–1970; when the data were analyzed by the

length of employment, the incidence of leukemia was only significantly elevated among workers employed for <1 year. Significant increases in incidence were also observed for pancreatic cancer in workers with a high probability of styrene exposure (incidence rate ratio of 2.2; 95% CI 1.1–4.5) and urinary bladder cancer in workers with the highest probability of exposure and employed for >1 year (incidence rate ratio of 2.1; 95% CI 1.1–4.1) (Kolstad et al. 1995). No significant alterations in the incidence of leukemia, lymphoma, or other cancers were observed in styrene workers at eight British reinforced plastic manufacturing facilities (Coggon et al. 1987). In a large international cohort of workers employed in the reinforced plastics industry (this cohort included the British cohort examined by Coggon et al. 1987 and the Danish cohort examined by Kolstad et al. 1993, 1994, 1995), no significant alterations in no excess in mortality from all cancer or cancer of the lymphatic and hematopoietic tissues were observed (Kogevinas et al. 1993, 1994). However, significant increases in the incidence of lymphatic and hematopoietic neoplasms were observed in workers with a latency of at least 10 years (relative risk [RR] 2.90; 95% CI 1.29–6.48 in workers with a latency of 10–19 years and RR 3.97; 95% CI 1.30–12.13 for workers with a latency of ≥20 years) and in workers exposed to ≥100 ppm styrene (RR 3.11; 95% CI 1.07–9.06 for workers exposed to 100–119 ppm; RR 3.08; 95% CI 1.04–9.08 for workers exposed to 120–199 ppm; RR 3.59; 95% CI 0.98–13.14 for workers exposed to ≥200 ppm), as compared to unexposed workers. An increase in the number deaths from malignant lymphomas was also observed in workers exposed to 120–199 ppm styrene (RR 7.15; 95% CI 1.21–42.11).

An increase in lymphatic leukemia (4 observed deaths versus 0.5 expected) in workers exposed to polymer extrusion fumes, solvents, and colorants, but was not found to be related to duration or level of exposure (Ott et al. 1980). In a follow-up to this study, which followed the workers for another 11 years (Bond et al. 1992), a nonsignificant increase in the number of deaths from lymphatic and hematopoietic tissue cancers (SMR 144; 95% CI 95–208) was observed. Statistically significant increases in the number of deaths from lymphatic and hematopoietic cancer were observed in workers exposed to 1–4 ppm styrene and a 15-year minimum latency (SMR 160; 95% CI 102–238); however, significant alterations were not found in workers exposed to ≥5 ppm or with longer latency periods. In another study of workers involved in the styrene production, polymerization, or processing, a statistically significant excess of lymphoma deaths (3 deaths observed versus 0.56 expected) was reported; 2 of the 3 deaths occurred in men <40 years of age who had been exposed for at least a year (Hodgson and Jones 1985). However, the lack of association with actual exposure levels or specific durations and the small number of observed deaths requires cautious interpretation. No significant alterations in the number of deaths from cancer were observed in workers (1960 subjects) exposed to styrene in a production and polymerization facility (Frentzel-Beyme et al. 1978). In a study of workers at a styrene-polystyrene manufacturing facility who

had at least 5 years of exposure, there were no significant increases in cause-specific mortality (Nicholson et al. 1978). However, when workers employed for <5 years were included in the analysis, there was an apparent increase in the number of deaths from lymphoma or leukemia (statistical analysis not conducted).

A number of older studies provide suggestive evidence of increased risk of lymphatic and hematopoietic cancers in workers at styrene-butadiene rubber manufacturing facilities (Matanoski and Schwartz 1987; Matanoski et al. 1990; McMichael et al. 1976; Meinhardt et al. 1982); however, these studies provided limited exposure data and did not adjust for contribution of 1,3-butadiene to the overall cancer risk. A case-control study (Matanoski et al. 1993, 1997; Santos-Burgoa et al. 1992) provides suggestive evidence that the increase in leukemia was due to exposure to 1,3-butadiene rather than to styrene exposure. However, increases in the risk of lymphosarcoma and myeloma were associated with styrene exposure (Matanoski et al. 1997). More recent studies of styrene-butadiene workers include adjustments for 1,3-butadiene exposure. A cohort mortality study conducted by Delzell and associates (Delzell et al. 1996; Macaluso et al. 1996) examined workers at many of the same styrene-butadiene rubber manufacturing facilities examined by Matanoski and associates and Meinhardt and associates. In this examination of 15,649 male synthetic rubber workers employed for at least 1 year at one of eight styrene-butadiene rubber manufacturing facilities in the United States or Canada, significant increases in deaths from leukemia were observed among hourly employees (SMR 143; 95% CI 104–191), particularly among workers employed for ≥10 and ≥20 years since hire (SMR 224; 95% CI 149–323) (Delzell et al. 1996). When workers were divided by year of hire and age at death, leukemia deaths were elevated in workers who were hired between 1950 and 1959 (SMR 200; 95% CI 122–310) and who were <55 years of age at the time of death (SMR 179; 95% CI 104–287). Using calculated estimates of exposure levels to 1,3-butadiene, styrene, and benzene, Macaluso et al. (1996) found that 75% of the cohort was exposed to 1,3-butadiene with a median cumulative exposure of 11.2 ppm-years, 83% of the cohort was exposed to styrene with a median cumulative exposure of 7.4 ppm-years, and 25% of the cohort was exposed to benzene with a cumulative exposure of 2.9 ppm-years. Among workers with leukemia, 86% had 1,3-butadiene exposure and 90% had styrene exposure; median cumulative exposure levels of 1,3-butadiene and styrene were about 3 times higher than the rest of the cohort. Workers with a cumulative exposure of 20–79 ppm 1,3-butadiene had a relative risk of leukemia mortality (after adjustment by race, age, and cumulative styrene exposure) that was 50% higher than workers with a cumulative exposure of 0.1–19 ppm and workers with a cumulative exposure of >80 ppm had a 70% higher relative risk than the low exposure group; the progressive of relative risk with increasing cumulative exposure was statistically significant. Although a similar progression was observed for

cumulative styrene exposure, the trend was not statistically significant. A follow-up to the Delzell et al. (1996) study, which tracked deaths for an additional 7 years (Sathiakumar et al. 2005), found similar results. A significant increase in deaths from leukemia was observed among hourly workers employed for >10 years and hired 20–29 years earlier (SMR 258; 95% CI 156–403). Increases in deaths for colorectal cancer among workers employed for >10 years and hired 20–29 years earlier (SMR 147; 95% CI 103–205) and deaths from prostate cancer among workers employed for <10 years and hired >30 years earlier (SMR 155; 95% CI 113–206). Significant increases deaths from leukemia were observed in workers involved in polymerization, coagulation, and finishing processes, maintenance workers, and laboratory workers; these workers had the highest potential exposure to 1,3-butadiene, styrene, and possibly dimethyldithiocarbamate. Subsequent analysis of these data using updated exposure assessments (Cheng et al. 2007; Delzell et al. 2001; Graff et al. 2005) found that the increased risk of leukemia was positively associated with 1,3-butadiene exposure. Positive associations between cumulative 1,3-butadiene exposure (ppm-years) and leukemia and between cumulative styrene exposure and leukemia were observed; the associations were only statistically significant at the highest cumulative exposure levels for 1,3-butadiene (≥362.2 ppm-years) or styrene (≥60.4 ppm) (Delzell et al. 2001). However, when the relative risks were adjusted for 1,3-butadiene and dimethyldithiocarbamate cumulative exposure, cumulative styrene exposure was no longer significantly associated with leukemia (Delzell et al. 2001; Graff et al. 2005). Because styrene, 1,3-butadiene, and dimethyldithiocarbamate exposure were correlated, it is difficult to separate the risks for each individual compound.

Several population-based studies have examined the possible carcinogenicity of styrene. A case-control study found a significant increase in prostate cancer (odds ratio of 5.5; 95% CI 1.4–21.8) and rectal cancer (odds ratio of 5.1; 95% CI 1.4–19.4) among workers with medium to high exposure to styrene (Gerin et al. 1998). Workers in the following professions were considered to have medium to high styrene exposure: motor vehicle painters, motor vehicle repairers, firemen, and plastic mould makers. Another study found a significant increase in the incidence of rectal cancer (SIR 3.11; 95% CI 1.14–6.77) among individuals with occupational exposure to styrene (Antilla et al. 1998). A limitation of both of these studies is the lack of exposure information, including levels of styrene and confounding exposure to other chemicals; thus, it is difficult to ascribe the increased cancer risks to styrene exposure. Loughlin et al. (1999) examined former students who attended a high school adjacent to synthetic styrene-butadiene rubber production facilities between 1963 and 1993 and found no significant alterations in deaths from lymphatic and hematopoietic cancer. Two studies have examined the possible association between styrene exposure and breast cancer. A case-control study by Cantor et al. (1995) found significant elevations in the risk of breast cancer among women possibly exposed to styrene in the workplace. Coyle

et al. (2005) found a significant higher incidence of age-adjusted breast cancer rate in men and women, women, and women ≥50 years of age and living in counties with EPA toxics release inventory (TRI) facilities with on-site releases of styrene. As with the other population-based studies, these studies did not monitor styrene levels or exposure to other potentially carcinogenic chemicals and thus provided limited information on the carcinogenic potential of styrene.

The carcinogenicity of styrene has been examined in three studies in rats (Conti et al. 1988; Cruzan et al. 1998; Jersey et al. 1978; Maltoni et al. 1982) and one study in mice (Cruzan et al. 2001). No significant increases in the incidence neoplastic lesions were observed in rats exposed to styrene concentrations as high as 1,000 ppm 6 hours/day, 5 days/week for 2 years (Cruzan et al. 1998). Similarly, exposure of female rats to 600 or 1,000 ppm styrene 6 hours/day, 5 days/week for 21 months did not result in styrene-related increases in the incidence neoplastic tumors (Jersey et al. 1978); a high incidence of chronic murine pneumonia in the control and 1,000 ppm male rats precludes the use of the male data for assessing the carcinogenic potential of styrene. There was a significant trend (Cochran-Armitage test conducted by ATSDR) for increased incidence of malignant mammary tumors in female rats exposed to styrene 4 hours/day, 5 days/week for 52 weeks (Conti et al. 1988); the incidences were 6/60, 6/30, 4/30, 9/30, 12/30, and 9/30 in the 0, 25, 50, 100, 200, and 300 ppm groups, respectively. No other significant increases in specific tumors were observed in this study (Conti et al. 1988; Maltoni et al. 1982). The findings of the Conti et al. (1988) study conflict with those of Cruzan et al. (1998), who found a concentration-related decrease in mammary tumors in female rats exposed to similar or higher styrene concentrations for a longer duration (20/60, 13/44, 9/43, 5/38, and 2/59 in female rats exposed to 0, 50, 200, 500, or 1,000 ppm, respectively). The decrease in body weight observed in the female rats exposed to ≥200 ppm may have influenced the occurrence of mammary tumors. In contrast to the results in rat studies, significant increases in the incidence of bronchioloalveolar carcinoma were observed in female mice exposed to 160 ppm 6 hours/day, 5 days/week for approximately 2 years (Cruzan et al. 2001). The incidences of bronchioloalveolar carcinoma were 0/50, 0/50, 2/50, 0/50, and 7/50 in the 0, 20, 40, 80, and 160 ppm female mice, respectively). Significant trends for increasing incidences of bronchioloalveolar adenoma were also observed for the male and female mice; the respective incidence of adenomas was 15/50, 21/50, 35/50, 30/50, and 33/50 in males and 6/50, 16/50, 16/50, 11/50, and 24/50 in females. The incidence of adenoma was significantly higher than controls in males exposed to 40, 80, or 160 ppm and in females exposed to 20, 40, or 160 ppm.

As discussed by IARC (2002) and Cruzan et al. (2002), the lung tumors observed in the mice are likely due to the *in situ* formation of styrene 7,8-oxide and 4-vinylphenol resulting in cytotoxicity and increased

cell proliferation. The relevance of these tumors to humans has been questioned due to species differences in the metabolism of styrene in the lungs. In rats and mice, Clara cells have the ability to metabolize styrene to styrene 7,8-oxide and 4-vinylphenol in the lung, whereas humans have limited ability to metabolize styrene to these metabolites in the lung. A physiologically based pharmacokinetic (PBPK) model predicted that the total amount of styrene oxide in the terminal bronchioles in mice is 10 times higher than in rats and 100-fold higher than in humans. In addition to these quantitative differences in the generation of styrene 7,8-oxide between rats and mice, there are qualitative differences in styrene metabolism. Mice produce higher levels of the R-enantiomer of styrene oxide, as compared to rats; the R-enantiomer has been shown to be more potent pneumotoxic than the S-enantiomer. The ratio of R- to S-enantiomers ranges from 2.2 to 2.87 in mice exposed to 20–160 ppm styrene and from 0.7 to 0.73 in rats exposed to 50–1,000 ppm. Thus, mice appear to be very sensitive to the induction of lung tumors and the mechanism of inducing lung tumors is not likely to be relevant to humans. Although the mechanism involved in the development of lung tumors in mice may not be applicable to humans, other mechanisms of styrene carcinogenicity may be relevant for humans.

3.2.2 Oral Exposure

No studies were located regarding health effects in humans after oral ingestion of styrene. Based on the animal data that follow, the oral toxicity of styrene in humans would be expected to be low to moderate.

3.2.2.1 Death

No deaths in humans from ingesting styrene have been reported in the evaluations of case studies (EPA 1989c; Gosselin et al. 1984; NIOSH 1983).

The approximate reported oral LD_{50} for male and female rats was 5,000 mg/kg (Wolf et al. 1956). A 100% survival rate and 100% mortality rate were reported in rats exposed to single oral doses of styrene (observation period 2 weeks) at 1,600 and 8,000 mg/kg, respectively (Spencer et al. 1942). Death in this study was mainly due to pronounced irritation of the esophagus and stomach. In another study, female mice were given a single oral dose of 1,350 mg/kg styrene on the 17th day of pregnancy (Ponomarkov and Tomatis 1978). After weaning, the progeny received the same dose once per week. The treatment was suspended after 16 weeks due to high mortality among the progeny (including both males and females). Fifty percent of the males and 20% of the females had died after 20 weeks, despite the suspension of treatment at week 16. The cause of death was liver necrosis and lung congestion. A high mortality rate was reported in 40 female rats exposed to 250 mg/kg/day styrene for 52 weeks (Conti et al.

1988). Mortality was significantly elevated in male and female rats administered styrene by gavage at a dosage level of 2,000 mg/kg/day for 78 weeks (NCI 1979b). In this study, mortality was unaffected at dosage levels of 500 and 1,000 mg/kg/day in male and female rats. Male mice administered styrene at doses of 150 or 300 mg/kg/day for 78 weeks showed increased mortality; however, the female mice did not.

The highest reliable LOAEL values and LD_{50}s values in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding endocrine, metabolic, musculoskeletal, or dermal/ocular effects in humans or animals after oral exposure to styrene.

For the following systemic effects resulting from oral exposure to styrene, the highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to styrene.

Severe lung congestion was observed in mice that were the offspring of dams given a single oral dose of styrene at 1,350 mg/kg on the 17th day of gestation and that continued to receive the same dose once per week after weaning (Ponomarkov and Tomatis 1978). The lung congestion was noted following 16 weeks of styrene administration. No respiratory effects were observed in rats exposed to 35 mg/kg/day styrene in drinking water for 105 weeks (Beliles et al. 1985).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to styrene.

No cardiovascular effects were observed in rats chronically exposed to 35 mg/kg/day in drinking water (Beliles et al. 1985).

Table 3-3 Levels of Significant Exposure to Styrene - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat	1 d (GO)				5000 (LD50)	Wolf et al. 1956 Styrene	
Neurological								
2	Rat	once (GO)			200 M (increased dopamine receptor binding)		Agrawal et al. 1982 Styrene	
3	Rat (Wistar)	14 d 1 x/d (GO)			100 M[b] (impaired learning)		Husain et al. 1985 Styrene	
Developmental								
4	Rat (Sprague-Dawley)	Gd 11 (GO)		300			Daston et al. 1991 Styrene	
5	Rat (Sprague-Dawley)	2 x/d Gd 6-15 (GW)		300 F			Murray et al. 1978 Styrene	
INTERMEDIATE EXPOSURE								
Immuno/ Lymphoret								
6	Rat (UF)	5 d/wk 4 wk (GO)		196 M	294 M (impaired immune response)		Dogra et al. 1992 Styrene	
7	Mouse (Swiss)	5 d/wk 4 wk (GO)		23 M	30 M (impaired immune response)		Dogra et al. 1992 Styrene	

Table 3-3 Levels of Significant Exposure to Styrene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
8	Rat	90 d 1 x/d (GO)			200 M (increased dopamine receptor binding)		Agrawal et al. 1982 Styrene	
9	Rat (Long- Evans)	5 d/wk 8 wk (GO)			500 M (impaired learning)		Bushnell 1994 Styrene	
10	Rat	15 d 1 x/d (G)			906 M (increased serotonin and noradrenaline and decreased monoamine oxidase levels)		Husain et al. 1980 Styrene	
11	Rat (Wistar)	15 days (GO)		250 F			Khanna et al. 1994 Styrene	
Reproductive								
12	Rat	90 d (continuous) (W)		35			Beliles et al. 1985 Styrene	
13	Rat	60 d 6 d/wk 1 x/d (GO)		200 M		400 M (marked degeneration of seminiferous tubules, decreased spermatozoa)	Srivastava et al. 1989 Styrene	

Table 3-3 Levels of Significant Exposure to Styrene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
14	Rat	Ld 1-21 (GO)		200 M	400 M (altered testicular enzyme levels and decreased spermatozoa counts)		Srivastava et al. 1992a Styrene	
15	Rat (Wistar)	6 d/wk pnd 1-61 (GO)		100 M	200 M (decreased testes weight and spermatozoa counts)		Srivastava et al. 1992b Styrene	
16	Rat (NS)	Gd 1-21, Gd 1- Ld 14-21, or Ld 1- Ld 14-21 (GO)			200 (increased dopamine receptor binding)		Zaidi et al. 1985 Styrene	
Cancer								
17	Mouse	16 wk 1 d/wk (GO)				1350 (CEL: lung tumors)	Ponomarkov and Tomatis 1978 Styrene	
CHRONIC EXPOSURE								
Death								
18	Rat	78 wk 5 d/wk 1 x/d (GO)				2000 (decreased survival in males and females)	NCI 1979b Styrene	

Table 3-3 Levels of Significant Exposure to Styrene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
19	Rat	105 wk 7 d/wk (W)	Resp	35			Beliles et al. 1985 Styrene	
			Cardio	35				
			Gastro	35				
			Hemato	35				
			Musc/skel	35				
			Hepatic	35				
			Renal	35				
			Dermal	35				
			Other	35				
20	Rat	120 wk 1 d/wk 1 x/d (GO)	Hepatic	500			Ponomarkov and Tomatis 1978 Styrene	
			Renal	500				
21	Dog	561 d 1 x/d (GO)	Hemato	200	400 (Heinz body formation)		Quast et al. 1979 Styrene	
Cancer								
22	Mouse	78-103 wk 5 d/wk 1 x/d (GO)				300 (CEL: lung tumors)	NCI 1979b Styrene	

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

b The acute-duration oral MRL of 0.1 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post-natal day; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s)

Figure 3-2 Levels of Significant Exposure to Styrene - Oral

Acute (≤14 days)

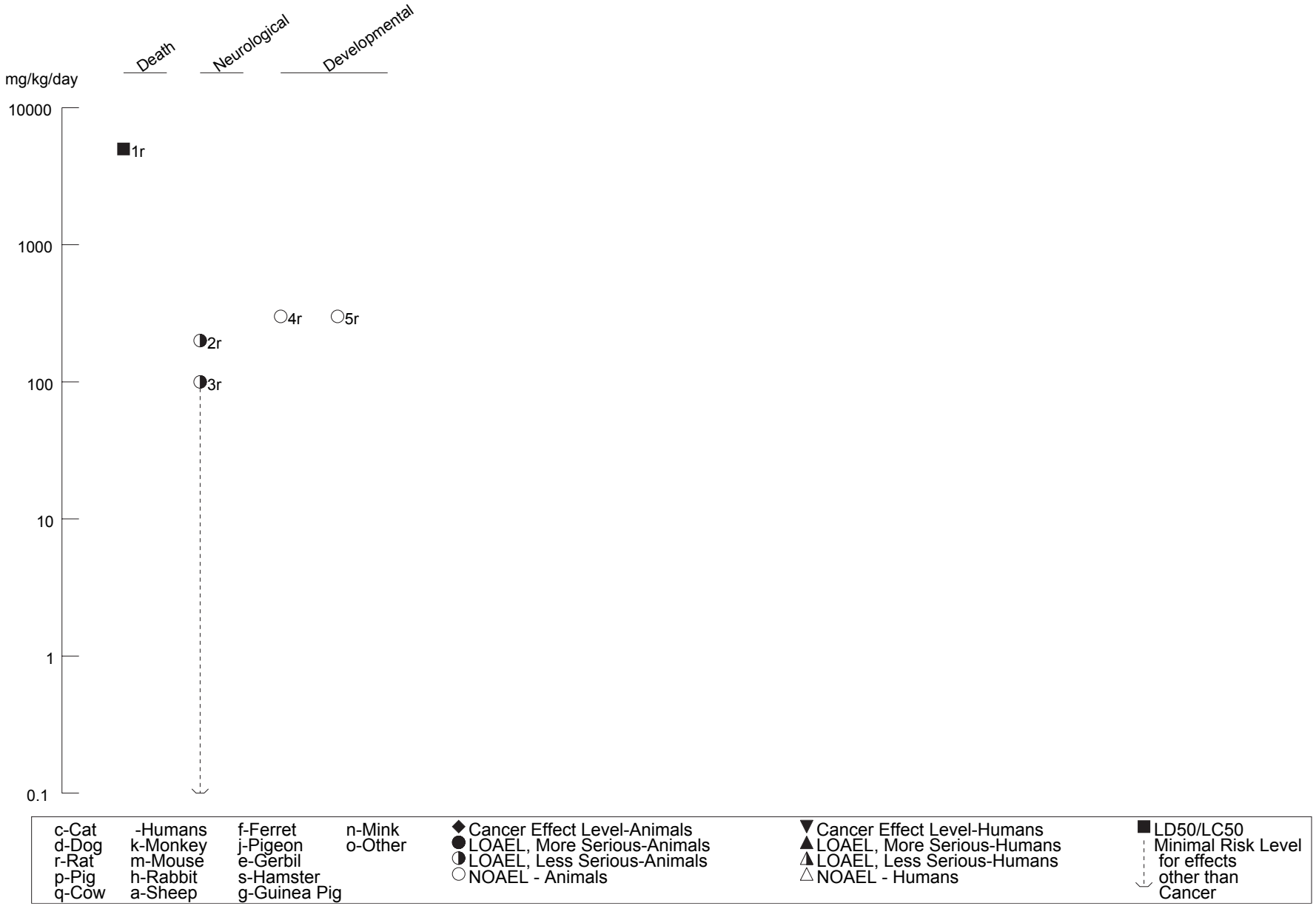
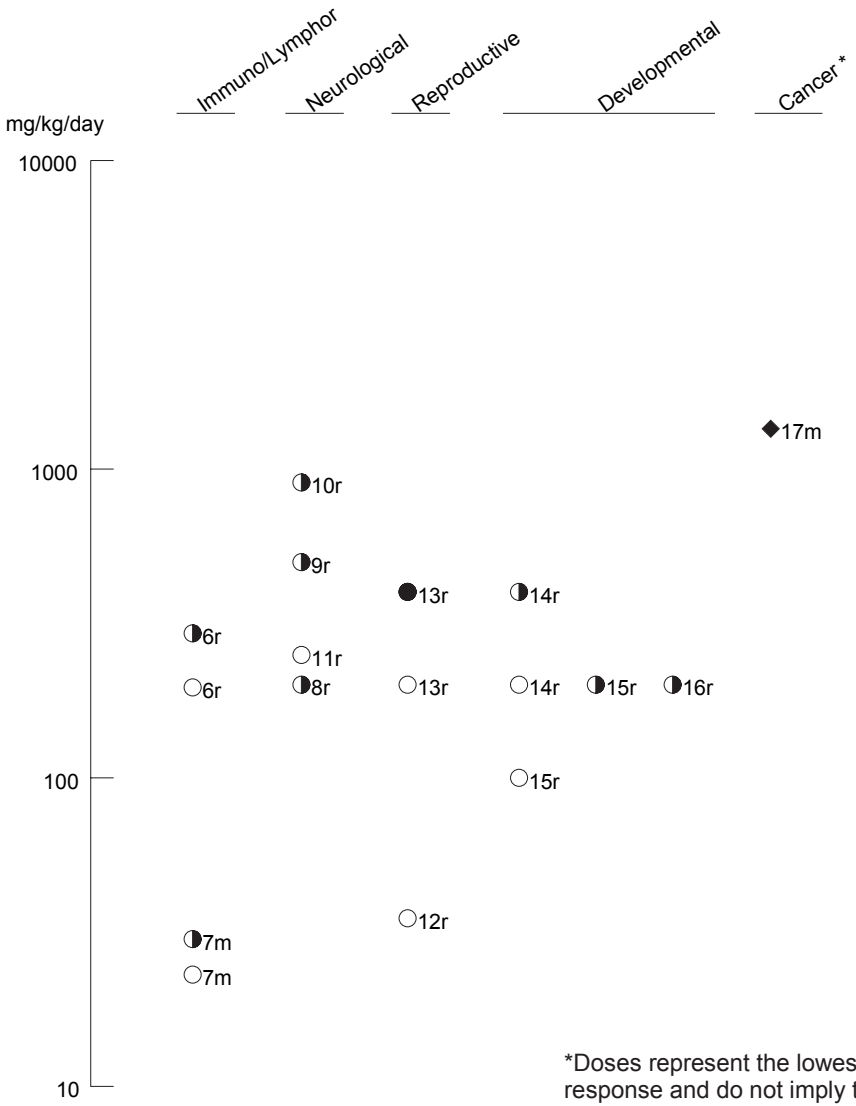


Figure 3-2 Levels of Significant Exposure to Styrene - Oral *(Continued)*

Intermediate (15-364 days)



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

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

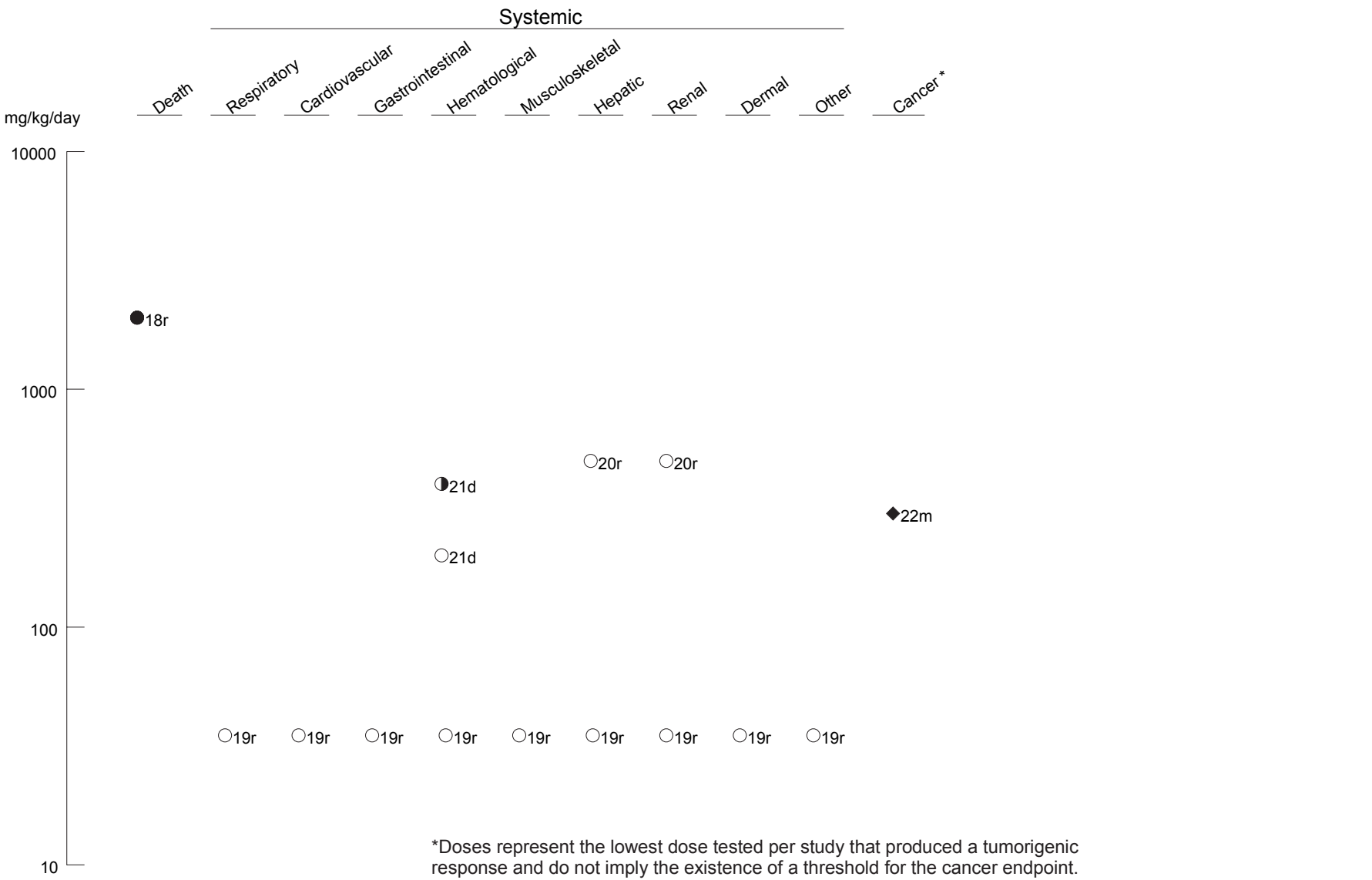
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

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

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

Figure 3-2 Levels of Significant Exposure to Styrene - Oral *(Continued)*

Chronic (≥365 days)



Gastrointestinal Effects. Abdominal pain was reported by 11% of the residents of two apartment buildings exposed to elevated levels of styrene in drinking water for 3 days (Arnedo-Pena et al. 2003). The concentration of styrene in the water was 900 μg/L and the dose was estimated to be 0.026 mg/kg/day. Based on other symptoms and the higher prevalence of symptoms among residents living near the contaminated water tank, it is likely that some of the observed effects were due to inhalation exposure of styrene vapors from the repair of a firewater tank adjacent to the drinking water tank.

No gastrointestinal effects were observed in rats chronically exposed to 35 mg/kg/day styrene in drinking water (Beliles et al. 1985).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to styrene.

Intra-erythrocytic Heinz bodies were regularly detected in a dose-related manner in male and female dogs chronically exposed to 400 or 600 mg/kg/day groups and sporadically in females in the 200 mg/kg/day group (Quast et al. 1979). There were occasional decreased red blood cell counts, hemoglobin levels, and erythrocyte sedimentation rates in males and females in the 600 mg/kg/day groups. Increased hemosiderin deposits and intranuclear inclusions in liver were noted in animals dosed with 600 mg/kg/day. This was probably secondary to the effects on the red blood cells. The formation of intra-erythrocytic Heinz bodies was readily reversible upon discontinuing the administration of styrene in the 600 mg/kg/day group after 470 days of exposure. No hematological effects were observed in rats chronically exposed to 35 mg/kg/day (Beliles et al. 1985).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to styrene.

Some animal studies have reported hepatic effects; however, the inconsistency of the findings and poor reporting of the data preclude drawing conclusion on the hepatotoxicity of orally administered styrene. Small areas of focal necrosis was observed in the livers of rats administered 400 mg/kg styrene in groundnut oil 6 days/week for 100 days (Srivastava et al. 1982). Because the incidence or statistical analysis data were not reported, it is not possible to determine whether 400 mg/kg is an adverse effect level. This study also found alteration in mitochondrial and microsomal enzymes at 200 and 400 mg/kg;

the significance of these alterations in the absence of histological damage is not known. An increase in liver weights was observed in rats administered 400 or 677 mg/kg via gavage 5 days/week for 6 months (Wolf et al. 1956); no histological alterations were observed. Although the alterations in the liver weight were considered slight at 400 mg/kg and moderate at 677 mg/kg, the magnitude of the change and statistical significance is not known; slight and moderate alterations in body weight were also observed at these dose levels. Hepatic glutathione content was reduced in rats orally administered 900 mg/kg styrene for 7 consecutive days (Das et al. 1981); the toxicological significance of this effect is not known. As noted above, increased numbers of hemosiderin deposits and intranuclear crystalline inclusions were reported in the hepatocytes of dogs orally administered 600 mg/kg/day of styrene by gavage for 316 days (Quast et al. 1979). This was presumably secondary to Heinz body formation, and no other hepatic histological effects were in this study. No hepatic effects were observed in rats exposed to 35 mg/kg/day styrene in drinking water for 105 weeks (Beliles et al. 1985) or in rats administered 500 mg/kg styrene 1 day/week for 120 weeks (Ponomarkov and Tomatis 1978).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to styrene.

A decrease in renal glutathione content and decreased glutathione-S-transferase activity was noted in rats orally administered 900 mg/kg styrene for 7 days (Das et al. 1983). Growth depression and slightly increased kidney weight were reported in female rats administered 400 and 667 mg/kg, 5 days/week for 6 months (Wolf et al. 1956); the magnitude and statistical significance of the effect were not reported. Histopathological examination of kidney tissue showed no abnormalities; thus, the changes in organ weight were not considered adverse. In another study, female rats and mice were exposed to 1,350 mg/kg/day of styrene on the 17th day of gestation; the offspring were also administered styrene, by gavage, 1 day/week for 120 weeks. No statistically significant increases in the incidence of kidney lesions were observed in rats exposed to 500 mg/kg (Ponomarkov and Tomatis 1978). No histological alterations were observed in the kidneys of rats chronically exposed to 35 mg/kg/day styrene in drinking water (Beliles et al. 1985).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to styrene.

The World Health Organization (WHO 1983) reviewed a Russian study conducted by Sinitskij in which styrene was fed to 36 rabbits at doses of 250 mg/kg for 58 days, 5 mg/kg for 216 days, and 0.5 mg/kg for 202 days. Impairment of the immunological defense system was indicated by a nearly total suppression of leukocyte phagocytic activity. Although no statistical analysis was provided, the data showed a dose-response relationship for both the severity of the effect and the time of onset. Similarly, impaired host resistance was observed in mice exposed to 30 mg/kg/day and infected with encephalomyocarditis or a rodent strain of malaria and rats exposed to 294 mg/kg/day and infected with a rodent hookworm parasite (Dogra et al. 1992).

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to styrene.

Neurobehavioral effects and alterations in neurochemicals have been observed in animal studies. Significant learning impairment was observed in an operant behavioral test in rats administered 500 mg/kg styrene in corn oil, 5 days/week for 8 weeks (Bushnell 1994). A reversal of the effect was not observed 1 year after exposure termination. Another study found significantly increased mean percent avoidance response, indicative of impaired learning, in rats administered 100 or 200 mg/kg/day styrene for 14 days (Husain et al. 1985). No alterations in foot shock-induced aggressive behavior or amphetamine-induced motor activity were observed in young rats administered via gavage 250 mg/kg/day styrene for 15 days (Khanna et al. 1994). However, significant alterations were observed in similarly exposed rats maintained on a low protein diet (8% casein versus 20% in normal diet).

Significant increases in serotonin levels in the hypothalamus, hippocampus, and midbrain were observed in rats administered 200 mg/kg/day for 14 days (Husain et al. 1985); no alterations in dopamine or noradrenaline levels were observed. Exposure to a higher dose (906 mg/kg/day) for 15 days resulted in increases in serotonin and noradrenalin in brain tissue (Husain et al. 1980). Neither study found significant alterations in brain dopamine levels. Another study found a significant increase in dopamine receptor binding, as assessed using labeled spiroperidol binding, in rats administered 200 or 400 mg/kg/day for 1 day or 90 days (Agrawal et al. 1982).

A series of studies by Chen and associates (Chen et al. 2007, 2008; Yang et al. 2008) examined the ototoxicity of styrene following gavage administration to rats. A dose-related increase in loss of outer hair cells was observed in rats exposed to 200–800 mg/kg/day styrene 5 days/week for 3 weeks (Chen et

al. 2007). At 400 mg/kg/day styrene 5 days/week for 3 weeks, 51.4% of the outer hair cells in the middle cochlear region were damaged (Yang et al. 2008). In rats exposed to 800 mg/kg/day for various durations, damage to the outer hair cells was not observed at durations shorter than 5 days; however, damage to Deiters cells, which support the outer hair cells, was evident after 3 days of exposure (Chen et al. 2007). As with the loss of outer hair cells, a dose-related increase in hearing threshold shifts, as measured by auditory brainstem response, was observed at 200–800 mg/kg/day. At frequencies of 10 and 20 kHz, a 100 mg/kg/day increase in styrene dose resulted in an additional 5 dB threshold shift. Because this study did not use a control group, a LOAEL value cannot be identified; however, Chen et al. (2008) noted that no losses of cochlear hair cells or hearing were observed in rats administered 100 mg/kg/day styrene 5 days/week for 24 weeks.

The highest NOAEL and LOAEL values for neurological effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to styrene.

Marked degeneration in the seminiferous tubules and decreased spermatozoa were observed in rats administered 400 mg/kg styrene via gavage 6 days/week for 60 days (Srivastava et al. 1989). No adverse reproductive effects were observed in a three-generation reproduction study in which rats were exposed to 35 mg/kg/day in drinking water (Beliles et al. 1985). In another study, marked degeneration of seminiferous tubules and decreased spermatozoa counts were observed in adult rats administered 400 mg/kg styrene via gavage 6 days/week for 60 days (Srivastava et al. 1989). Significant decreases in sorbitol dehydrogenase and acid phosphatase levels and increases in lactate dehydrogenase, glucose-6-phosphate dehydrogenase, β-glucuronidase, and γ-glutamyl transpeptidase levels were also observed at this dose level; the investigators considered these enzymes to be markers for testicular function.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in rats in the acute and intermediate duration categories are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to styrene.

No developmental effects were observed in the offspring of rats receiving a single gavage dose of 300 mg/kg on gestational day 11 (Daston et al. 1991) or in rats administered 300 mg/kg/day (150 mg/kg administered twice daily) on gestational days 6–15 (Murray et al. 1978).

Other developmental studies have focused on the impaired development of the reproductive system or neurodevelopmental effects. Decreases in spermatozoa counts (measured on postnatal days 61 and 91) were observed in offspring of rats administered to 400 mg/kg styrene on lactation days 0–21; no effects were observed at 200 mg/kg/day (Srivastava et al. 1992a). However, decreases in spermatozoa counts were observed in rats exposed to 200 mg/kg 6 days/week on postnatal days 1–61 (Srivastava et al. 1992b). Both studies found significant alterations in testicular enzyme levels at the same dose level as spermatozoa effects; these enzymes were considered markers of testicular function. A decrease in dopamine receptor binding, as assessed using labeled spiroperidol, was observed in the offspring of rats administered to 200 mg/kg/day styrene throughout gestation and lactation or only during lactation, but was not observed in rat pups only observed during gestation (Zaidi et al. 1985). This decrease in receptor binding was attributed to an increase in the number of dopamine receptors rather than an alteration in binding affinity. Impaired amphetamine-induced locomotor activity and apomorphine-induced stereotypy were also observed in the pups exposed during gestation and lactation.

The highest NOAEL value for developmental effects is recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding cancer effects in humans after oral exposure to styrene.

Investigations of the carcinogenic potential of styrene in animals after oral exposure have yielded variable results. No significant alterations in the incidence of neoplastic tumors were observed in rats exposed to gavage doses as high as 250 mg/kg 4–5 days/week for 52 weeks (Conti et al. 1988; Maltoni et al. 1982) or 2,000 mg/kg 5 days/week for 78–103 weeks (NCI 1979b) or in rats exposed to 35 mg/kg/day styrene in drinking water for 2 years (Beliles et al. 1985). In contrast, significant increases in the incidence of lung tumors were observed in mice receiving gavage doses of 300 mg/kg 5 days/week for 78–103 weeks (NCI 1979b). The incidences of bronchioloalveolar carcinoma in male mice were 0/20, 3/44, and 5/43 in mice exposed to 0, 150, or 300 mg/kg, respectively, and the respective combined incidences of bronchiolo-alveolar carcinoma and adenoma in male mice were 0/20, 6/44, and 9/43. The incidence of bronchiolo-alveolar carcinoma in the 300 mg/kg group was similar to the incidence in untreated historical controls

(12%), but lower than the incidence in historical vehicle controls 0/40; however, the National Cancer Institute (NCI 1979b) noted that the incidence in historical vehicle controls is based on too small a number of animals for meaningful use of historical control data. Two studies conducted by Ponomarkov and Tomatis (1978) examined the carcinogenicity of styrene following gestation and postnatal exposure. In the offspring of mice administered 1,350 mg/kg on gestation day 17 with continued exposure of the weanling mice to this dose level (1 day/week) for 16 weeks, a significant increase in lung tumors was observed during the 100-week observation period; this dose was also associated with treatment-related toxicity and mortality. In the second study, the mice were exposed to 300 mg/kg on gestation day 17 followed by exposure to 300 mg/kg for 120 weeks (1 day/week) beginning at weaning. No significant alterations in tumor incidence were observed.

3.2.3 Dermal Exposure

No studies were located regarding health effects in humans after dermal exposure to styrene.

3.2.3.1 Death

No studies were located regarding lethality in humans or animals after dermal exposure to styrene.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, endocrine, or renal effects in humans or animals after dermal exposure to styrene.

Dermal Effects. Marked irritation with denaturation of the skin was noted when styrene was applied in small amounts over a 4-week period to the shaved abdomen of rabbits at 20,000 mg/kg total dose) (Spencer et al. 1942).

Ocular Effects. Moderate conjunctival irritation and transient corneal injury of the eyes were observed when undiluted styrene was tested in rabbit eyes (Wolf et al. 1956). The effects were produced immediately (within 3 minutes) by a single administration of two drops (about 0.1 mL) and persisted throughout the 7-day observation period.

No studies were located regarding the following health effects in humans or animals after dermal exposure to styrene:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

The genotoxicity of styrene has been examined in numerous *in vivo* studies of workers and laboratory animals; these data are summarized in Table 3-4. Chromosomal damage, DNA strand breaks, and mutagenic effects have frequently been studied in workers exposed to styrene in the production of reinforced plastic products and styrene/polystyrene production. In general, these studies are limited by the fact that workers in these industries are often exposed to chemicals other than styrene, such as methylene chloride and epoxide resins, and many studies did not control for potential confounding factors such as age, sex, and smoking status. Chromosomal aberrations have been reported in numerous studies of workers exposed to styrene for 1–25 years in reinforced plastic operations (Anwar and Shamy 1995; Artuso et al. 1995; Hogstedt et al. 1979; Mäki-Paakkanen et al. 1991; Meretoja et al. 1977, 1978; Somorovská et al. 1999; Tomanin et al. 1992); however, other studies have not found significant increases in chromosomal aberrations (Andersson et al. 1980; Hansteen et al. 1984; Jablonicka et al. 1988; Mäki-Paakkanen 1987; Nordenson and Beckman 1984; Thiess et al. 1980; Vodicka et al. 2004; Watanabe et al. 1981). The results of the Artuso et al. (1995) and Tomanin et al. (1992) studies provide suggestive evidence that the occurrence of chromosomal aberrations is concentrated-related. Significant increases in chromosomal aberrations alterations were observed in high exposure groups (20–326 or 27–104 ppm), but not in workers exposed to lower exposure levels (0.5–24 ppm). As with the occurrence of chromosomal aberrations, mixed results have been observed in studies of sister chromatid exchange (Andersson et al. 1980; Artuso et al. 1995; Hallier et al. 1994; Hansteen et al. 1984; Karakaya et al. 1997; Laffon et al. 2002; Mäki-Paakkanen 1987; Mäki-Paakkanen et al. 1991; Watanabe et al. 1981; Yager et al. 1993) and micronuclei formation (Anwar and Shamy 1995; Hogstedt et al. 1983; Karakaya et al. 1997; Laffon et al. 2002; Mäki-Paakkanen et al. 1991; Nordenson and Beckman 1984; Tomanin et al. 1993; Vodicka et al. 2004) in styrene workers. Other genotoxicity studies in styrene workers have found significant increases in glycophorin A mutations (Bigbee et al. 1996; Compton-Quintana et al. 1993),

Table 3-4. Genotoxicity of Styrene *In Vivo*

Species (test system)	End point	Results	Reference
Human studies			
Human lymphocytes	Chromosomal aberrations	+	Meretoja et al. 1977
Human lymphocytes	Chromosomal aberrations	+	Meretoja et al. 1978
Human lymphocytes	Chromosomal aberrations	+	Hogstedt et al. 1979
Human lymphocytes	Chromosomal aberrations	+	Anwar and Shamy 1995
Human lymphocytes	Chromosomal aberrations	+	Artuso et al. 1995
Human lymphocytes	Chromosomal aberrations	+	Mäki-Paakkanen et al. 1991
Human lymphocytes	Chromosomal aberrations	+	Tomanin et al. 1992
Human mononuclear leukocytes	Chromosomal aberrations	+	Somorovská et al. 1999
Human lymphocytes	Chromosomal aberrations	–	Thiess et al. 1980
Human lymphocytes	Chromosomal aberrations	–	Andersson et al. 1980
Human lymphocytes	Chromosomal aberrations	–	Watanabe et al. 1981
Human lymphocytes	Chromosomal aberrations	–	Nordenson and Beckman 1984
Human lymphocytes	Chromosomal aberrations	–	Hansteen et al. 1984
Human lymphocytes	Chromosomal aberrations	–	Maki-Paakkanen 1987
Human lymphocytes	Chromosomal aberrations	–	Jablonicka et al. 1988
Human lymphocytes	Chromosomal aberrations	–	Vodicka et al. 2004
Human lymphocytes	Sister chromatid exchange	+	Yager et al. 1993
Human lymphocytes	Sister chromatid exchange	+	Laffon et al. 2002
Human lymphocytes	Sister chromatid exchange	+	Karakaya et al. 1997
Human lymphocytes	Sister chromatid exchange	+	Artuso et al. 1995
Human lymphocytes	Sister chromatid exchange	+	Hallier et al. 1994
Human lymphocytes	Sister chromatid exchange	+	Andersson et al. 1980
Human lymphocytes	Sister chromatid exchange	–	Mäki-Paakkanen et al. 1991
Human lymphocytes	Sister chromatid exchange	–	Hansteen et al. 1984
Human lymphocytes	Sister chromatid exchange	–	Watanabe et al. 1981
Human lymphocytes	Sister chromatid exchange	–	Maki-Paakkanen 1987
Human lymphocytes	Micronuclei	+	Nordenson and Beckman 1984
Human lymphocytes	Micronuclei	+	Hogstedt et al. 1983
Human lymphocytes	Micronuclei	+	Laffon et al. 2002
Human lymphocytes	Micronuclei	–	Karakaya et al. 1997

Table 3-4. Genotoxicity of Styrene *In Vivo*

Species (test system)	End point	Results	Reference
Human lymphocytes	Micronuclei	–	Anwar and Shamy 1995
Human lymphocytes	Micronuclei	–	Mäki-Paakkanen et al. 1991
Human lymphocytes	Micronuclei	–	Tomanin et al. 1992
Human lymphocytes	Micronuclei	–	Vodicka et al. 2004
Human erythrocytes	Mutations in glycophorin A	+	Bigbee et al. 1996
Human erythrocytes	Mutations in glycophorin A	+	Compton-Quintana et al. 1993
Human lymphocytes	HPRT mutations	±	Vodicka et al. 1995
Human mononuclear leukocytes	DNA Single strand breaks	+	Somorovská et al. 1999
Human lymphocytes	DNA Single strand breaks	+	Shamy et al. 2002
Human lymphocytes	DNA Single strand breaks	+	Mäki-Paakkanen et al. 1991
Human leukocytes	DNA Single strand breaks	+	Walles et al. 1993
Human lymphocytes	DNA Single strand breaks	+	Vodicka et al. 1995
Human lymphocytes	DNA Single strand breaks	–	Vodicka et al. 2004
Human lymphocytes	Unscheduled DNA synthesis	+	Pero et al. 1982
Laboratory animal studies			
Mouse bone marrow	Chromosomal aberrations	–	Sbrana et al. 1983
Rat bone marrow	Chromosomal aberrations	–	Sinha et al. 1983
Mouse bone marrow	Sister chromatid exchange	±	Simula and Priestly 1992
Mouse spleen, lung, erythrocytes	Sister chromatid exchange	+	Kligerman et al. 1992, 1993
Mouse bone marrow, liver cells, and alveolar macrophages	Sister chromatid exchange	+	Conner et al. 1980
Mouse bone marrow	Sister chromatid exchange	±	Simula and Priestly 1992
Rat lymphocyte	Sister chromatid exchange	+	Kligerman et al. 1992, 1993
Mouse bone marrow and polychromatic erythrocytes	Micronuclei	±	Norppa 1981
Mouse bone marrow	Micronuclei	±	Simula and Priestly 1992
Mouse bone marrow	Micronuclei	–	Engelhardt et al. 2003
Mouse spleen, lung, erythrocytes	Micronuclei	–	Kligerman et al. 1992, 1993
Mouse bone marrow	Micronuclei	–	Simula and Priestly 1992
Rat lymphocyte	Micronuclei	–	Kligerman et al. 1992, 1993
Mouse bone marrow and lymphocytes	DNA single strand breaks	–	Vodicka et al. 2001a
Mouse kidney, liver, lung, testes, and brain	DNA	+	Walles and Orsen 1983

Table 3-4. Genotoxicity of Styrene *In Vivo*

Species (test system)	End point	Results	Reference
Mouse liver	Unscheduled DNA synthesis	–	Clay 2004

– = negative result; + = positive result; ± = weakly positive result; DNA = deoxyribonucleic acid

DNA single strand breaks (Mäki-Paakkanen et al. 1991; Shamy et al. 2002; Somorovská et al. 1999; Walles et al. 1993; Vodicka et al. 1995), and increases in unscheduled DNA synthesis (Pero et al. 1982).

Studies in laboratory animals have found significant increases in the occurrence of sister chromatid exchange (Conner et al. 1980; Kligerman et al. 1992, 1993; Simula and Priestly 1992). However, the results for chromosomal aberrations (Sbrana et al. 1983; Sinha et al. 1983), micronuclei formation (Engelhardt et al. 2003; Kligerman et al. 1992, 1993; Norppa 1981; Simula and Priestly 1992), DNA single strand breaks (Vodicka et al. 2001a), and unscheduled DNA synthesis (Clay 2004) have been weakly positive or negative.

Styrene has been tested for genotoxic potential in a variety of *in vitro* systems, as summarized in Table 3-5. In the absence of metabolic activation, styrene has not produced gene mutations in *Salmonella typhimurium* (DeMeester et al. 1981; Dunkel et al. 1985; Vainio et al. 1976) or *Escherichia coli* (Dunkel et al. 1985); mixed results have been found in the presence of metabolic activation. Increases in chromosomal aberrations (Jantunen et al. 1986) and sister chromatid exchange (Norppa et al. 1983) have been found in human lymphocytes in the absence of metabolic activation.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The uptake of styrene following inhalation exposure in humans and animals is rapid (Ramsey and Andersen 1984; Ramsey and Young 1978; Ramsey et al. 1980; Withey and Collins 1979; Withey and Karpinski 1985). Pulmonary retention of inhaled styrene in humans is approximately 2/3 of the administered concentrations (Engstrom et al. 1978a, 1978b). For example, male human subjects were exposed to styrene in inspired air during 30-minute rest and three 30-minute work periods on a bicycle ergometer. The mean uptake was approximately 63% (range was 59–70%) of the amount of inspired styrene. In exercising volunteers exposed to 50 ppm styrene for 2 hours, an average of 66.5% of the inhaled styrene was absorbed (Johanson et al. 2000). Another study in volunteers exposed to 50 ppm styrene for 2 hours during exercise calculated that 64% of the styrene was absorbed (Norstöm et al. 1992). Exposures of rats to styrene concentrations of 50–2,000 ppm for 5 hours yielded blood uptakes that showed a continued and increasing rapid absorption, proportional to the styrene air level (Withey and

Table 3-5. Genotoxicity of Styrene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (two strains, plate incorporation method)	Gene mutation	+	–	Vainio et al. 1976
S. typhimurium (three strains, plate incorporation method)	Gene mutation	–	–	Vainio et al. 1976
S. typhimurium (three strains, vapor exposure – disiccator test)	Gene mutation	+	–	DeMeester et al. 1981
S. typhimurium (four strains, vapor exposure – disiccator test)	Gene mutation	–	–	DeMeester et al. 1981
S. typhimurium (five strains, preincubation method)	Gene mutation	–	–	Dunkel et al. 1985
Escherichia coli (one strain, preincubation method)	Gene mutation	–	–	Dunkel et al. 1985
Mammalian cells:				
Human lymphocytes	Sister chromatid exchange	No data	+	Norppa et al. 1983
Human lymphocytes	Chromosomal aberrations	No data	+	Jantunen et al. 1986

— = negative result; + = positive result

Collins 1979). Plateau levels of styrene in rats' blood were reached within 6–8 hours during exposures ranging from 80 to 1,200 ppm styrene for up to 24 hours (Ramsey and Young 1978).

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to styrene.

The absorption of styrene from the gastrointestinal tract was rapid and complete in rats deprived of food overnight and administered, via gavage, 9.3 mg/kg styrene in aqueous solution. A peak blood level of 6 μg/mL was reached in a few minutes. There was a much slower uptake of the styrene administered in vegetable oil (Withey 1976). Styrene administered in vegetable oil at a total dose of 32.61 mg produced a peak level of 12 μg/mL. This was reached at about 100 minutes (Withey 1976).

3.4.1.3 Dermal Exposure

Limited data indicate that absorption of styrene via the dermal route is probably low compared to absorption via other routes. When liquid styrene was applied to the forearms of male subjects, the absorption rate was estimated to be 9–15 mg/cm^2/hour (Dutkiewicz and Tyras 1968). By contrast, the rate of absorption through human skin was very low (1 ± 0.5 μg/cm^2/minute) in subjects who dipped one hand into liquid styrene (Berode et al. 1985). The higher absorption rate reported by Dutkiewicz and Tyras (1968) likely included the disappearance rate of the solvent from the surface of the skin (Guillemin and Berode 1988). Riihimaki and Pfaffli (1978) demonstrated that in humans, dermal exposure to moderate concentrations of styrene vapor (300 and 600 ppm) resulted in percutaneous penetration corresponding to approximately 0.1–2% of the amount estimated to be absorbed from the respiratory tract. Similarly, Limasset et al. (1999) did not find significant differences in the levels of urinary metabolites in workers wearing total protective equipment (insulating suit and respiratory mask) and those wearing a respiratory mask only.

Although absorption of styrene applied to the abdomen of rabbits was reported, there was no information on absorption rates (Spencer et al. 1942). Dermal exposure of rats to a neat solution of styrene resulted in peak blood levels of 5.3 μg/mL within 1 hour of exposure (Morgan et al. 1991).

3.4.2 Distribution

A blood:air partition coefficient of 40.2 and fat:air partition coefficient of 3,476 were calculated for rats (Gargas et al. 1989). Fisher et al. (1997) calculated a human blood:air partition coefficient of 69.74 and a breast milk:blood partition coefficient of 2.17.

In a study of 81 adults without occupational exposure to styrene, average blood styrene levels were 0.221 µg/L; in comparison, blood styrene levels in reinforced plastics industry workers were 1,068–1,590 µg/L at the end of workshift and 60–119 µg/L in the morning after exposure (Brugnone et al. 1993).

3.4.2.1 Inhalation Exposure

Inhalation studies in both humans and animals resulted in the widespread distribution of styrene with the highest concentration in adipose tissue.

Three humans were exposed to 8–20 ppm styrene which resulted in a mean daily uptake of 193–558 mg styrene (Engstrom et al. 1978b). The concentration of styrene in adipose tissue was 2.8–8.1 mg/kg at the beginning of the week and 4.7–11.6 mg/kg at the end of the week. The authors estimated the half-life of styrene in the subcutaneous fat of humans to be about 72 hours. Subsequent studies by this author confirmed this estimate and reported the half-life of styrene in adipose tissue to be 2–5 days (Engstrom et al. 1978a).

Fiberglass factory workers exposed to >50 ppm of styrene for 8-hour work shifts had blood styrene levels which ranged from 120 to 684 µg/L at the end of the shift (Apostoli et al. 1983). The concentrations of urinary MA and phenylglyoxylic acid (PGA) were 133–2,100 and 107–685 mg/L, respectively. These levels were also determined at the end of the work-shift. Distribution of styrene was also studied in adult men exposed to about 70 ppm of styrene for 2 hours during light physical exercise (Wigaeus et al. 1983). Blood styrene reached a level of approximately 2,000 µg/L after 75 minutes. The concentration of styrene in adipose tissue was about 5,000 µg/kg after 30–90 minutes of exposure.

Rats were exposed for 5 hours to styrene at concentrations ranging from 50 to 2,000 ppm (Withey and Collins 1979). Tissue concentrations of styrene in the heart, liver, lung, kidney, spleen, brain, and perirenal fat demonstrated different patterns of distribution as the dose increased. The styrene concentration in perirenal fat was 10 times greater than in other organs. The largest amounts of styrene were found in the subcutaneous fat of male rats exposed to about 45 ppm of radioactively labeled styrene

in the inspired air for 1–8 hours (Carlsson 1981). The concentration increased steadily during the first 4 hours of exposure. Styrene concentrations in brain tissue and muscles were about 70% of the arterial blood value. Other investigators (Ramsey and Andersen 1984; Ramsey and Young 1978; Savolainen and Pfaffli 1978; Withey 1976) demonstrated that higher levels of styrene in adipose tissue increase with higher exposures to styrene. Styrene was found to distribute to the fetuses of pregnant rats after inhalation exposure, but at concentrations much lower than those measured in maternal organs and tissues (Withey and Karpinski 1985).

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to styrene.

An oral dose of 20 mg/kg of ^{14}C styrene was administered to male and female rats (Plotnick and Weigel 1979). Tissue levels peaked at 4 hours or earlier after dosing. Less than 10% of the administered dose was found in the stomach, small intestine, and large intestine 8 hours after dosing. The kidney had the highest concentration of radioactivity at all time intervals, with decreasing amounts in the liver and pancreas. Fat tissue showed increased levels after 2 hours. All tissue levels were below 1 μg/g at 24 hours and at 48 and 72 hours were below the limit of detection. In rats receiving a gavage dose of 800 mg/kg styrene, blood styrene levels peaked during the first 30 minutes of exposure and remained fairly steady for the first 6 hours. A similar pattern was observed when the rats were dosed with 800 mg/kg/day for 6 days; 24 hours after administration of the sixth dose, styrene was not detected in the blood (Chen et al. 2007). A linear relationship between styrene dose and blood styrene levels was observed following single doses of 100–800 mg/kg (Chen et al. 2007).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to styrene.

Immersion of rats' tails in pure liquid styrene for 1 hour resulted in styrene levels in the liver and brain that were estimated to be between 50 and 70% of the concentrations found in the same organs after 4-hour inhalation exposure to a vapor concentration of 11.8 g/m^3 (Shugaev 1969). A skin:air partition coefficient of 91.9 was calculated for rat skin (Mattie et al. 1994).

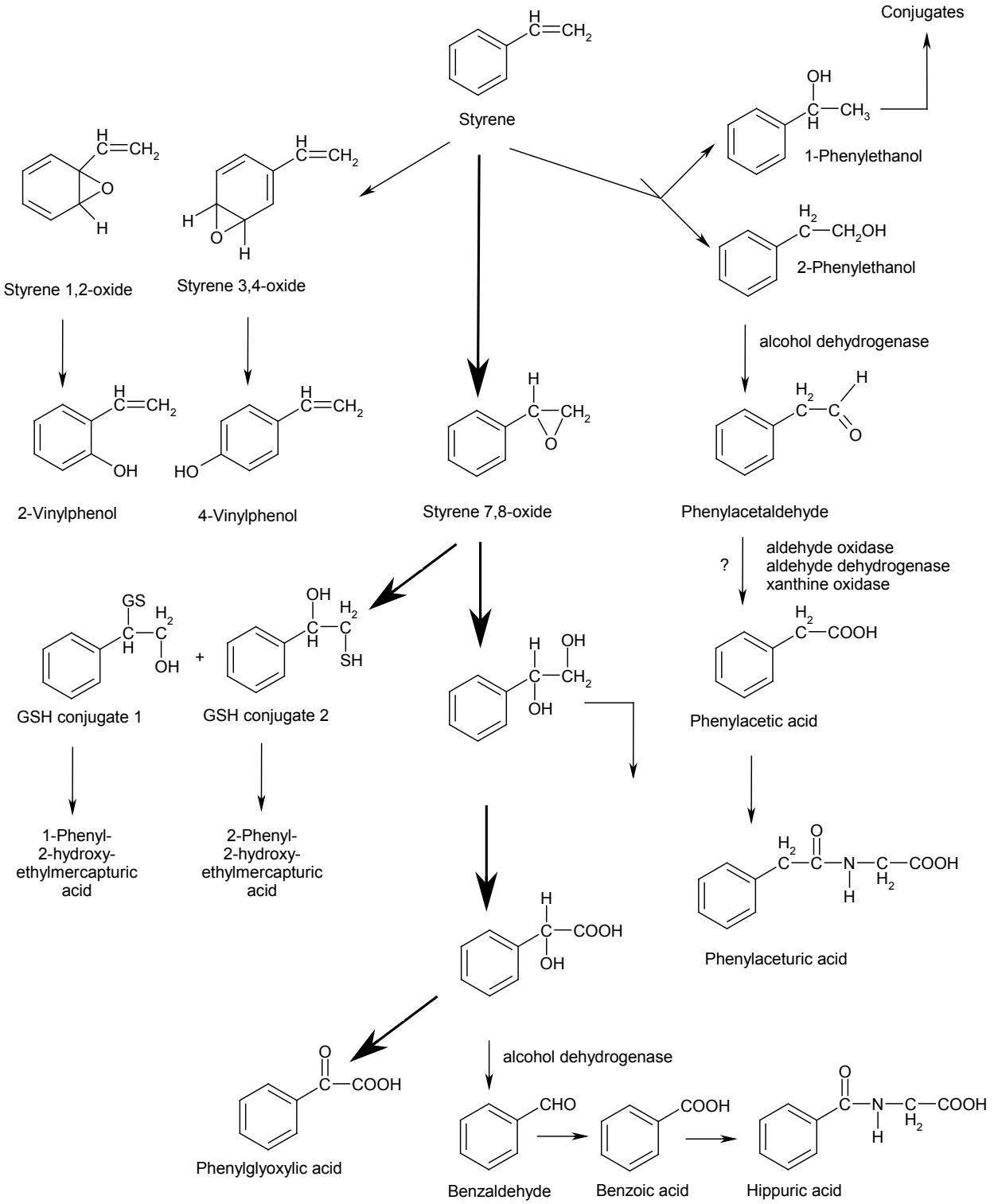
3.4.3 Metabolism

There have been numerous *in vivo* studies, conducted primarily via inhalation, and *in vitro* studies that address the metabolism of styrene in humans and animals. There are several metabolic pathways for styrene (Cruzan et al. 2002; IARC 2002; Sumner and Fennel 1994), as illustrated in Figure 3-3. The primary pathway is oxidation of the side chain by cytochrome P450 to form styrene 7,8-oxide. Styrene oxide is predominantly metabolized by epoxide hydrolase to form styrene glycol; the styrene glycol is subsequently converted to mandelic acid, phenylglyoxylic acid, and hippuric acid. Styrene 7,8-oxide can also be conjugated with glutathione to ultimately form phenylhydroxylethylmercapturic acids. A minor pathway of styrene metabolism involves the formation of phenylacetaldehyde from styrene 7,8-oxide or cytochrome P450 conversion of styrene to pheylethanol and subsequent metabolism to phenylacetic acid. An alternative minor pathway involves ring oxidation resulting in the production of styrene 3,4-oxide, which is further metabolized to 4-vinylphenol.

As summarized by Cruzan et al. (2002), over 95% of the styrene urinary metabolites excreted by humans are derived from styrene glycol (mandelic acid, phenylglyoxylic acid, hippuric acid) compared to 49–59% in mice and 68–72% in rats. In mice and rats, 25–35% of the metabolites are derived from glutathione conjugation (mercapturic acids). The remaining metabolites derive from phenylacetic acid production (12–22% in mice and 3–5% in rats) and ring oxidation (4–8% in mice and <1% in rats). Trace amounts of mercapturic acids (DePalma et al. 2001) and 4-vinylphenol (Manini et al. 2002, 2003) have also been detected in humans; both metabolites each account for <1% of the total styrene metabolites.

The liver is the primary site of styrene metabolism and the source of styrene oxide in the blood (Cruzan et al. 2005). However, styrene is metabolized in other tissues, particularly the lung and nasal cavity following inhalation exposure, and it is this localized metabolism that results in the observed toxicity and/or carcinogenicity in these tissues. Studies in humans, mice, and rats indicate that styrene metabolism is concentration-dependent. At air concentrations of <200–300 ppm, most of the inhaled styrene is metabolized, only small amounts are exhaled unchanged, and there is little accumulation (Filser et al. 1993; Ramsey and Andersen 1984). At concentrations >300 ppm, metabolism was pregressively limited by metabolic capacity and was saturated (V_{max}) at 700 ppm in rats and at 800 ppm in mice (Filser et al. 1993). Löf and Johanson (1993) estimated that metabolic saturation occurs at 100–200 ppm in humans; however, a subsequent analysis by this group (Jonsson and Johanson 2002) found that the V_{max} was 40% higher.

Figure 3-3. Scheme for Styrene Metabolism in Humans and Animals



GSH = glutathione

Source: Adapted from IARC 2002; Manini et al. 2002; Sumner and Fennel 1994

Comparisons of cytochrome P450, epoxide hydrolase, and glutathione S-transferase activity in the liver and lungs of rats and mice demonstrated 2–15-fold higher activities in the liver (Mendrala et al. 1993). In both tissues, previous exposure to styrene did not result in a dose-related increase in enzyme activity. In contrast, cytochrome P450 from human lung has a very limited ability to metabolize styrene to styrene oxide (Carlson et al. 2000; Nakajima et al. 1994); the capacity was 100-fold lower than in rat lung microsomes (Cruzan et al. 2002).

A number of cytochrome P450 isozymes have the capacity to catalyze styrene to styrene oxide. In human livers, CYP2B6 was the most active isoform; the activities of CYP1A2 and CYP2E1 were about half that of CYP2B6 (Nakajima et al. 1993). Kim et al. (1997) found that CYP2E1 was the main isoform at low styrene concentrations and CYP2B6 at high styrene concentrations. In mice and rats, the CYP1A1 and CYP2B1, respectively, were the most active isoforms in the liver (Nakajima et al. 1993). In the lungs, CYP2F1 was the most active isoform in human (Nakajima et al. 1994) lung microsomes. In mice and rat lung and nasal cavity microsomes, CYP2F2 and CYP2E1 are the predominant isoforms (Hynes et al. 1999).

Studies by Mendrala et al. (1993) compared the kinetic constants of cytochrome P450 from the livers of humans, mice, and rats. The affinity of cytochrome P450 for styrene (based on K_m valves) was similar for the three species. However, the mouse had the greatest capacity to form styrene 7,8-oxide from styrene based on the V_{max} values and relative liver and body size, and humans had the lowest capacity. In contrast, marked differences in the K_m values for epoxide hydrolase were found between species; the K_m values were 0.01, 0.74, and 0.13-0.23 mmol for humans, mice, and rats, respectively. These results suggest that humans have a greater affinity to metabolize styrene 7,8-oxide and is more efficient at low levels of styrene oxide, as compared to rodent species.

Styrene oxide exists as two enantiomeric forms (R) and (S). As with other aspects of styrene metabolism, species differences in the ratio of R enantiomer and S enantiomer have been detected. In human liver samples, the R:S ratio was 0.15 at low styrene concentrations (0.016 mM) and 1.4 at high styrene concentrations (1.1 mM) (Wenker et al. 2001). In mouse and rat liver microsomes (incubated with 2 mM styrene), the R:S ratio was 0.57 and 1.18, respectively (Hynes et al. 1999). In the lungs, the R:S ratio was 2.4 and 0.52 for mice and rats, respectively.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Several studies have demonstrated that styrene is almost totally excreted as urinary metabolites in humans, and at higher doses, the elimination profile indicates saturation of metabolic excretion or processes (Ramsey and Young 1978; Ramsey et al. 1980). Most of the inhaled styrene is excreted in urine as MA and PGA. In a study of the excretion of styrene and its metabolites resulting from a 100-ppm/8-hour inhalation exposure, 2.6% of the total uptake was excreted as unchanged styrene in exhaled air (Guillemin and Berode 1988). The metabolites MA, PGA, and hippuric acid were excreted in the urine at 56.9, 33, and 7.5% of the absorbed dose, respectively. In exercising volunteers exposed to 50 ppm styrene for 2 hours, 0.7–2.2% of the retained dose was exhaled as unchanged styrene (Johanson et al. 2000). Peak levels of styrene in the urine were measured immediately after exposure termination, whereas urinary excretion of MA and PGA peaked at 2 hours after exposure termination. MA excretion accounted for 6–29% of the estimated retained dose and PGA excretion accounted for 4–6%; the halftime excretion rates of MA and PGA were 2.2–4.2 and 3.5–13.9 hours, respectively. Phenylaceturic acid and hippuric acid was also detected in the urine samples collected 2 hours after exposure termination. At this time point, MA account for 73% of the total excreted metabolites, PGA 18%, phenylaceturic acid 4.5%, and hippuric acid 5.7%. In styrene workers exposed to 29–42 ppm styrene, both R-mandelic acid and S-mandelic acid were detected in the urine (Hallier et al. 1995). The ratio of R- to S-mandelic acid ranged from 0.7 to 1.2 in 19 of the 20 workers; in the last worker, the ratio was 2.2.

An alternative pathway for the metabolism of styrene 7,8-oxide is conjugation with glutathione, resulting in the excretion of mercapturic acids. Low levels of mercapturic acids have been detected in workers exposed to an unspecified amount of styrene (Maestri et al. 1997a). The mean concentrations of styrene metabolites were 580 mg/g creatinine mandelic acid, 174 mg/g creatinine phenylglyoxylic acid, 1.517 mg/g N-acetyl-S-(1-phenyl-2-hydroxyethyl)-cysteine S-enantiomer, 0.0637 mg/g N-acetyl-S-(1-phenyl-2-hydroxyethyl)-cysteine R- enantiomer, and 1.519 mg/g N-acetyl-S-(2-phenyl-2-hydroxyethyl)-cysteine. Another study of styrene workers (exposure level of 29–41 ppm) only detected styrene-specific mercapturic acid in 1 of 20 workers (Hallier et al. 1995). Similarly, in volunteers exposed to 50 ppm for 2 hours during exercise, N-acetyl-S-(2-phenyl-2-hydroxyethyl)-cysteine was not detected in urine samples collected up to 5 hours after exposure termination (Norström et al. 1992).

In volunteers exposed to 80 ppm styrene, styrene is cleared from the blood in a biphasic manner, indicating a two-compartment pharmacokinetic model. The half-lives for the rapid and slow clearance

phases are 0.58 and 13.0 hours, respectively. The half-life of styrene in subcutaneous adipose tissue of humans is 2–5 days (Engstrom et al. 1978a). The quantities of the major metabolites of styrene in urine compared with the quantity of styrene eliminated unchanged in expired air indicated that approximately 97% is cleared by the metabolic route (Ramsey et al. 1980).

Another human inhalation study determined that between 59 and 66% of inhaled styrene (50–200 ppm) was retained after a 4–8-hour exposure (Guillemin and Bauer 1979). Urinary elimination of MA was biphasic with a half-life for the first phase of 4 hours and for the second phase, 25 hours. These findings were comparable to those reported by Engstrom et al. (1976). The half-life of urinary elimination of PGA was determined to be 11 hours. This was regarded by the authors as being the first phase of elimination since MA is a precursor of PGA.

A lactational transfer pharmacokinetic model developed by Fisher et al. (1997) predicted that exposure to 50 ppm styrene would result in 0.650 mg styrene being ingested by a nursing infant over a 24-hour period.

Styrene is almost totally excreted as urinary metabolites in animals. The blood elimination curve for rats is biphasic exponential at 80 and 200 ppm styrene over 6 hours. For exposures >600 ppm exposure levels for 6 hours duration), a nonlinear blood elimination curve following Michaelis-Menten kinetics was observed. In going from 80 to 1,200 ppm (a 15-fold increase) the area under the blood concentration curves increases by 112-fold (Ramsey and Young 1978; Young et al. 1979). Rats exposed to 50–2,000 ppm styrene by inhalation for 5 hours exhibited a dose dependent biphasic pattern of elimination (Withey and Collins 1979).

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to styrene.

Styrene was rapidly excreted in the urine of male and female rats administered 20 mg/kg of ^{14}C styrene with 90% of the dose detected in the urine within 24 hours of administration (Plotnick and Weigel 1979). Less than 2% of the dose was found in the feces. Detectable tissue levels were not found 48 and 72 hours after administration. In mice administered 200 mg/kg for 70 days, 26.4, 13.3, and 19.0% of urinary metabolites excreted on day 70 were mandelic acid, phenylglyoxylic acid, and hippuric acid (Sbrana et al. 1983). Approximately 80% of the dose was excreted in the first 24 hours.

3.4.4.3 Dermal Exposure

In a study of the absorption of liquid styrene applied to the forearms of male volunteers, about 13% of the absorbed dose was excreted as MA (Dutkiewicz and Tyras 1968).

No studies were located regarding excretion in animals after dermal exposure to styrene.

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987a). 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-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic

equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

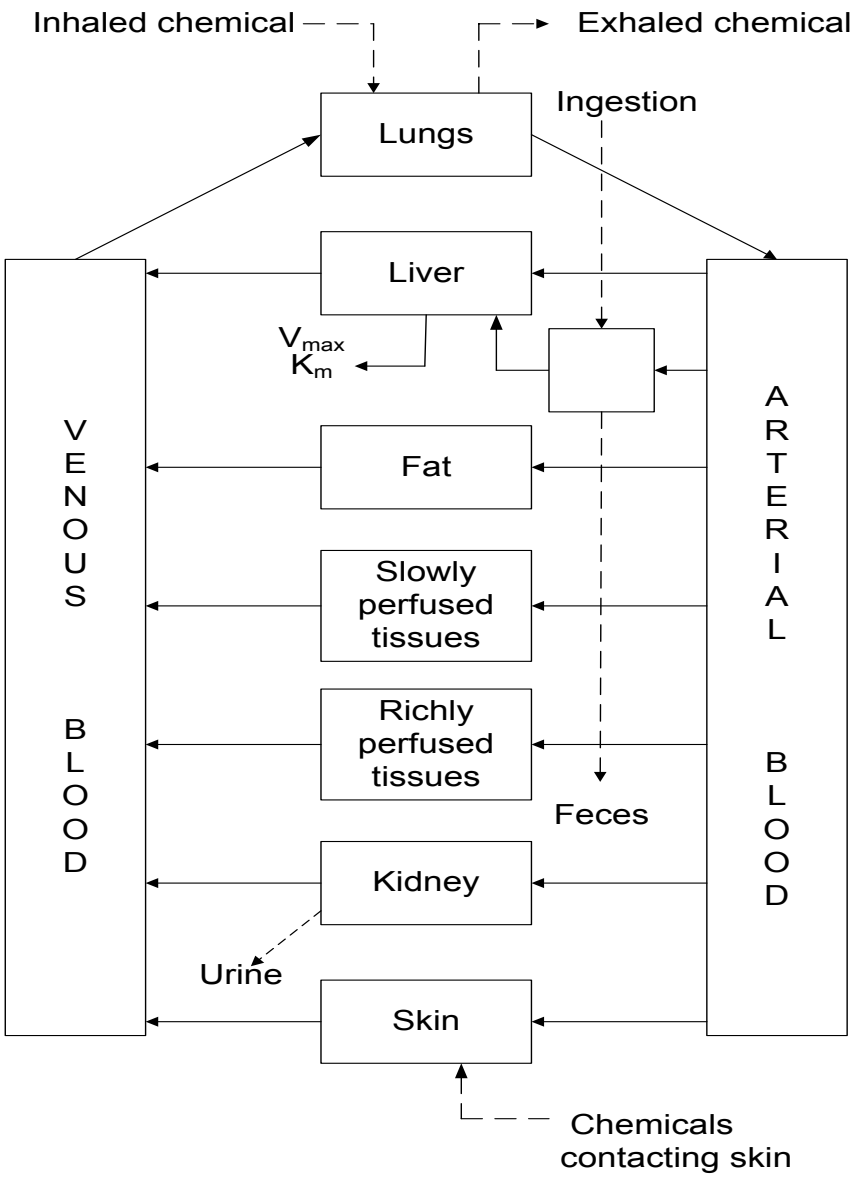
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

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

Several investigators have developed toxicokinetic models for styrene (Csanády et al. 1994, 2003; Jonsson and Johanson 2002; Leavens and Bond 1996). The Csanády et al. (1994, 2003) model is useful for evaluating the carcinogenic risk associated with inhalation exposure to styrene. As discussed in Section 3.2.1.7, species differences exist in the metabolism of styrene in the lungs of rats, mice, and humans; these differences result in increased sensitivity of mice. Jonsson and Johanson (2002) developed a population-based PBPK model for styrene, which decreased the intraindividual variability for estimating the metabolic capacity for styrene in humans. Leavens and Bond (1996) described initial work on developing a model for co-exposure to 1,3-butadiene and styrene in mice. Some of these models provide strong support for the observed differences in styrene toxicity between rats, mice, and humans. As discussed further in Section 3.5.3, some have primarily focused on the species differences in the metabolism of styrene and metabolic differences between rats, mice, and humans.

Figure 3-4. 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

3.4.5.1 Summary of PBPK Models

A number of investigators have developed toxicokinetic models for styrene. The earliest model was developed by Ramsey and Anderson (1984) to relate styrene exposure concentrations quantitatively to blood concentrations. A model developed by Csanády et al. (1994, 2003) is useful in describing the blood/tissue time course of styrene and styrene oxide in rats, mice, and humans following multiple routes of administration. A model developed by Sarangapani et al. (2002) expands these models and adds a description of styrene and styrene oxide levels in multiple compartments of the respiratory tract; this model is described below.

Additionally, Jonsson and Johanson (2002) developed a population-based PBPK model for styrene, which decreased the intraindividual variability for estimating the metabolic capacity for styrene in humans. Leavens and Bond (1996) described initial work on developing a model for co-exposure to 1,3-butadiene and styrene in mice.

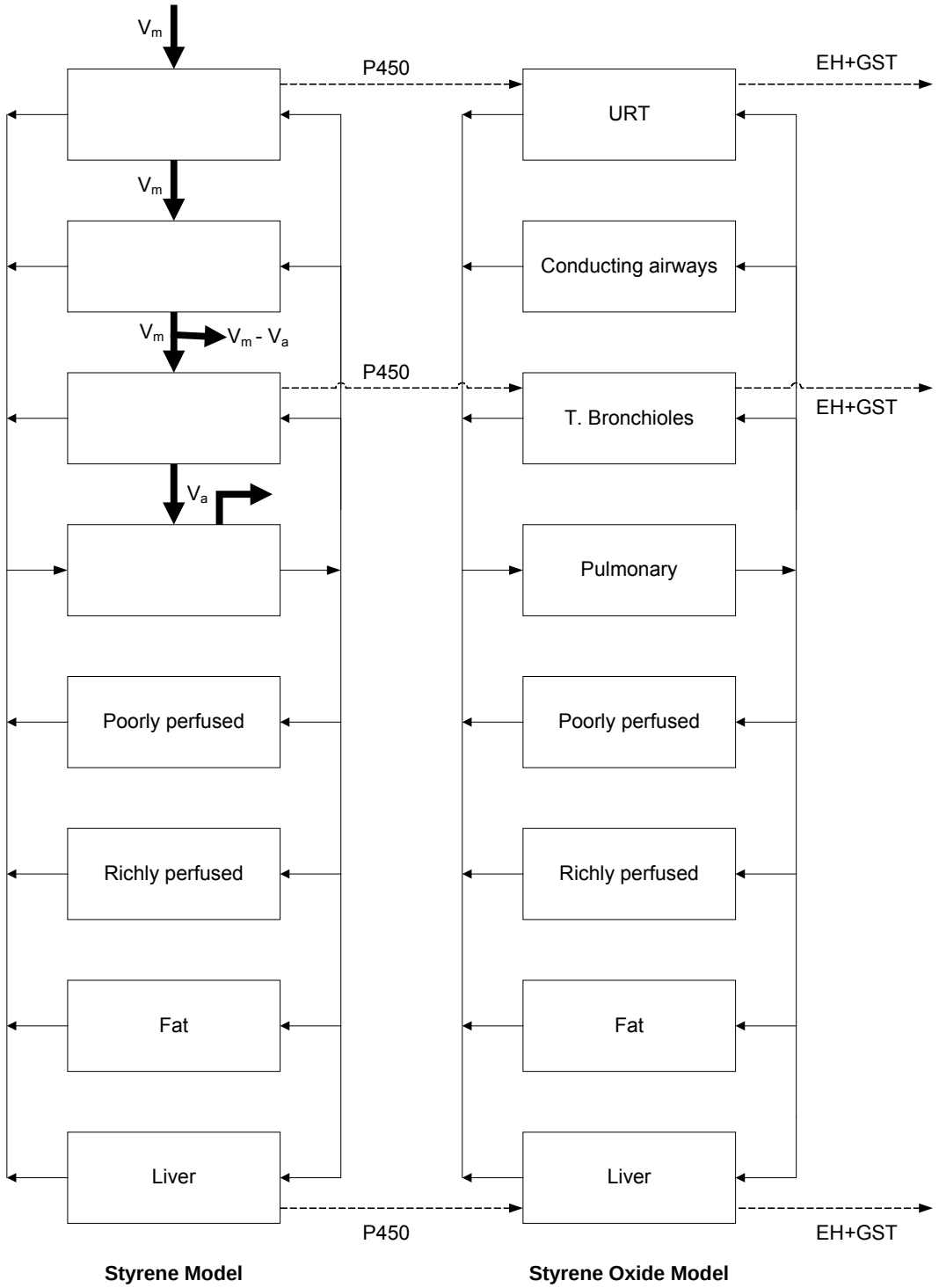
3.4.5.2 Discussion of Model

Risk assessment. The Sarangapani model quantifies the observed differences in the occurrence of lung tumors between rats, mice, and humans.

Description of the model. The Sarangapani model is a mode of action based PBPK model developed to predict blood, liver, and respiratory tract tissue (particularly the terminal bronchioles) levels of styrene and styrene oxide and allow for interspecies extrapolations. The model has a nested architecture with a model for styrene and a linked submodel for styrene oxide. Both models consist of four respiratory tract tissue compartments (upper respiratory tract, conducting airways, terminal bronchioles, and pulmonary) and systemic tissue compartments for liver, fat, richly perfused tissue, and poorly perfused tissue. The metabolism of styrene to styrene 7,8-oxide and the detoxification of styrene 7,8-oxide by epoxide hydrolase and glutathione S-transferase was modeled to occur in the liver and selected regions of the lung. The styrene oxide formed in the parent model in any tissue compartment was passed to the corresponding tissue compartment in the metabolite submodel; the schematic of the PBPK model is presented in Figure 3-5. Inhalation was the only exposure route considered in this model.

Mass balance equations were used to account for the transport of styrene across the lumen and tissue subcompartments in the upper, conducting, and transitional airways and in the liver. Additionally mass

Figure 3-5. Styrene and Styrene Oxide Models used in the Sarangapani PBPK Model



EH = epoxide hydrase; GST = glutathione S-transferase; PBPK = physiologically based pharmacokinetic; T. Bronchioles = transitional bronchioles; URT = upper respiratory tract; Va = alveolar ventilation; Vm = minute ventilation or pulmonary ventilation;

Source: Sarangapani et al. 2002

balance equations were used to describe the production of styrene 7,8-oxide, elimination of styrene oxide, and kinetics of cytosolic glutathione in the liver and lung. Most of the physiological and flow parameters (Table 3-6) and respiratory tract-specific physiological parameters (Table 3-7) used in the model were obtained from the literature. Tissue volumes for the respiratory tract compartments were estimated by multiplying the appropriate surface areas with the tissue thickness. The kinetic constants used for hepatic and lung cytochrome P450, epoxide hydrolase, and glutathione S-transferase are presented in Table 3-8. Stereospecific kinetic parameters (Table 3-9) and steady-state concentrations of R-styrene oxide and S-styrene oxide were used to account for species differences in the stereospecific metabolism of styrene to styrene oxide.

Validation of the model. Ten independent data sets ranging from closed chamber data to concentration measurements of styrene and styrene oxide in multiple tissues following multiple routes of exposure were used to validate various dose metrics in the mouse, rat, and human. The model provided good fit across species and at multiple target sites, including the whole lung for both styrene and styrene oxide. The model was not validated for styrene and styrene oxide levels in the transitional bronchioles due to the lack of experimental data.

Target tissues. The model was used to predict steady-state styrene oxide levels in arterial blood and the terminal bronchioles.

Species extrapolation. The model predicted that the levels of styrene oxide in the transitional bronchioles are approximately 10- and 100-fold lower in rats and humans, as compared to mice, thus suggesting that humans would be 100-fold less sensitive than mice to styrene-induced lung tumors.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Styrene is rapidly absorbed through the respiratory tract (Ramsey and Andersen 1984; Ramsey and Young 1978; Ramsey et al. 1980; Withey and Collins 1979; Withey and Karpinski 1985) with a mean uptake of approximately 60–70% in humans (Johanson et al. 2000; Norström et al. 1992). A concentration-dependent uptake efficiency was found in the upper respiratory tract of rats and mice

Table 3-6. Physiological and Flow Parameters Used in the Sarangapani PBPK Model

Parameter	Mouse	Rat	Human
Body weight (g)	25	250	70,000
Tissue volume as fraction of body weight			
Liver	5.5	3.66	2.6
Richly perfused tissues	10	12.34	8.5
Poorly perfused tissues	70	70	60
Fat	7	6.5	21.4
Blood	7.5	7.5	7.5
Minute ventilation (mL/minute)	24	150	15,000
Pulmonary ventilation (mL/minute)	12–1	75–110	10,500
Cardiac output (mL/minute)	14	110	5,200
Tissue blood flow as fraction of cardiac output			
Liver	15–30	15–30	22.7
Richly perfused tissues	48	28.7	43
Fat	5.9	7	5.2
Upper airways	1.0	1.0	0.25
Conducting airways	0.5	2.1	0.75
Transitional airways	0.1	0.15	0.67
Partition coefficients for styrene			
Blood:air	40	40	48
Liver:blood	2	2	2
Fat:blood	87	87	50
Tissue:blood	1.3	1.3	1.3
Partition coefficients for styrene 7,8-oxide			
Blood:air	2,000	2,000	2,000
Liver:blood	1	1	1
Fat:blood	14	14	14
Tissue:blood	0.6	0.6	0.6
Styrene:styrene oxide tissue-phase diffusivity (cm^2/minute)	0.0002	0.0002	0.0002
Styrene:styrene oxide air-phase diffusivity (cm^2/minute)	6	6	6

Source: Sarangapani et al. 2002

Table 3-7. Respiratory Tract-Specific Physiological Parameters Used in the Sarangapani PBPK Model

Parameter	Mouse	Rat	Human
Tissue thickness (cm)			
Upper airway epithelium	0.005	0.005	0.005
Conducting airway epithelium	0.0025	0.0025	0.0025
Transitional airway epithelium	0.001	0.001	0.001
Pulmonary airway epithelium	0.0003	0.00025	0.0005
Mucus	0.0005	0.001	0.001
Upper airway submucosa	0.01	0.01	0.01
Conducting airway submucosa	0.005	0.005	0.005
Transitional airway submucosa	0.002	0.002	0.002
Surface area (cm^2)			
Upper airway compartment	2.7	13.2	138
Conducting airway compartment	8.87	48.3	2,000
Transitional airway compartment	0.48	5.5	,6220
Pulmonary airway compartment	500	3,400	540,000
Mass transfer coefficient (cm/min)			
Upper airway air-phase	7,200	7,200	1,980
Conducting airway air-phase	312	228	181
Transitional airway air-phase	1,136	481	158
Tissue liquid phase	32	16	19.2
Intracompartment clearance (cm^3/minute)	10	40	400
Lung microsomal protein (mg/mL)	3.8	3.8	3.8
Liver microsomal protein (mg/mL)	13	11	23
Lung cytosolic protein (mg/mL)	68	60	43
Liver cytosolic protein (mg/mL)	94	90	45

Source: Sarangapani et al. 2002

Table 3-8. Kinetic Parameters Used in the Sarangapani PBPK Model

Parameter	Mouse	Rat	Human
V_{max} Cytochrome P450 (nmol/minute/mL)			
Liver	200	50–150	50
Upper airway	183	98	50
Transitional airway	362	46.4	1.7
K_m Cytochrome P450 (nmol/mL)	10	10	10
V_{max} Epoxide hydrolase (nmol/minute/mL)			
Liver	200	250	900
Upper airway	250	250	500
Transitional airway	250	250	500
K_m Epoxide hydrolase (nmol/mL)	100	100	100
V_{max} Glutatione S-transferase (nmol/minute/mL)			
Liver	11,000	6,300	1,400
Upper airway	1,000	1,000	300
Transitional airway	1,000	1,000	300
K_m Glutathione S-transferase for styrene (nmol/mL)	2,500	2,500	2,500
K_m Glutathione S-transferase for styrene oxide (nmol/mL)	700	700	500
Liver glutathione basal concentration (nmol/mL)	8,300	6,300	6,000
Upper airway glutathione basal concentration (nmol/mL)	1,000	2,500	1,000
Transitional airway glutathione basal concentration (nmol/mL)	1,000	1,000	1,000
Glutathione production rate (per minute)	0.012	0.012	0.012

Source: Sarangapani et al. 2002

Table 3-9. Stereospecific Kinetic Parameters for Styrene and Styrene Oxide Metabolism in Rodents Used in the Sarangapani PBPK Model

	Mouse		Rat	
Parameter	R	S	R	S
V_{max} Cytochrome P450-liver (nmol/minute/mL)	108.3	91.7	33.8	59.2
V_{max} Cytochrome P450-terminal bronchioles (nmol/minute/mL)	211.8	88.2	130	250
K_m Cytochrome P450 (nmol/mL)	10	10	10	10
K_m Epoxide hydrolase, liver (nmol/mL)	66.7	133.3	570	151
K_m Epoxide hydrolase, terminal bronchioles (nmol/mL)	125	125	200	50
K_m Epoxide hydrolase (nmol/mL)	29	155	29	155
V_{max} Glutatione S-transferase-liver (nmol/minute/mL)	4,400	6,600	2,400	3,600
V_{max} Glutatione S-transferase-terminal bronchioles (nmol/minute/mL)	400	600	400	600
K_m Glutathione S-transferase for styrene oxide (nmol/mL)	700	2,000	700	2,000
K_m Glutathione S-transferase for glutathione (nmol/mL)	2,500	2,500	2,500	2,500

Source: Sarangapani et al. 2002

(Morris 2000). In rats, the uptake efficiency was 23.7% at 5 ppm and 10.1% at 200 ppm; in mice, uptake efficiency decreased from 41.7% at 5 ppm to 9.6% at 200 ppm. Based on the decreased uptake efficiency observed in rats and mice following exposure to the cytochrome P450 inhibitor, metyrapone, Morris (2000) suggested that styrene was metabolized *in situ* and this metabolism enhanced styrene uptake. In humans, blood styrene levels reached steady state after 75 minutes of exposure to 70 ppm (Wigaeus et al. 1983). The elimination of styrene from blood was biphasic, with a half-time of 1 minute for the rapid distribution phase and 40.8 minutes for the elimination phase. Styrene is rapidly distributed throughout the body with the highest concentrations found in adipose tissue. In rats, the styrene concentration in the adipose tissue was approximately 50-fold higher than in muscle; the biological half-time was 6.3 hours in adipose tissue and 2.4–2.0 hours in the blood, liver, kidney, spleen, muscle, and brain (Teramoto and Horiguchi 1979). In humans, styrene is primarily excreted in the urine as mandelic acid and phenylglyoxylic acid. The half-times of mandelic acid and phenylglyoxylic acid in the urine were 3.6 and 8.8 hours, respectively, in humans exposed to 70 ppm for 2 hours (Wigaeus et al. 1983); another study reported elimination half-times of 2.2–4.2 hours for mandelic acid and 3.5–13.9 hours for phenylglyoxylic acid following a 2-hour exposure to 50 ppm styrene (Johanson et al. 2000).

3.5.2 Mechanisms of Toxicity

A large number of studies have investigated the mechanism of styrene carcinogenic activity, particularly the increased susceptibility of mice. Increases in malignant lung tumors have been observed in mice exposed to 160 ppm 6 hours/day, 5 days/week for approximately 2 years (Cruzan et al. 2001) and following gavage exposure to 300 mg/kg/day administered 5 days/week (NCI 1979b); however, neoplastic tumors have not been observed in rats exposed to concentrations as high as 1,000 ppm 6 hours/day, 5 days/week for 2 years (Cruzan et al. 1998) or 2,000 mg/kg/day 5 days/week for 2 years (NCI 1979b), suggesting that mice are particularly sensitive. As reviewed by IARC (2002), Cohen et al. (2002), and Cruzan et al. (2002), genotoxic and nongenotoxic modes of action have been proposed. Although styrene itself does not appear to be DNA reactive, styrene 7,8-oxide is DNA reactive and has been shown to form stable N_2 and O_6 adducts of deoxyguanosine. Styrene oxide, DNA adducts, and genotoxic effects have been detected in humans, rats, and mice. Styrene has been shown to be mutagenic in bacteria, and exposure can result in increased frequency of sister chromatid exchange, chromosomal aberrations, micronucleated cells, and DNA strand breaks. However, elevated levels of blood styrene oxide do not explain the species differences in tumor formation. In humans, styrene 7,8-oxide is rapidly hydrolyzed by epoxide hydrolase as evidenced by the high levels of mandelic acid, phenylglyoxylic acid, and hippuric acid detected in the urine. Styrene 7,8-oxide is relatively stable in rats and mice, and

elevated levels have been detected in blood. The blood levels of styrene oxide in rats exposed to 1,000 ppm is 100-fold higher than the levels in mouse exposed to 20–40 ppm; however, tumors have not been detected in rats.

The nongenotoxic potential mode of action also implicates styrene 7,8-oxide and 4-vinylphenol (or its ring-oxidized metabolites) as the causative agents (Cruzan et al. 2002, 2005). The nongenotoxic mechanism involves cytotoxic damage to Clara cells in the lung. In the mouse lung, styrene is primarily metabolized by cytochrome P450, particularly the CYP2F2 isoform, in the Clara cell. The continued exposure to styrene 7,8-oxide and 4-vinylphenol results in Clara cell cytotoxicity, increased cell proliferation, bronchiolar epithelial hyperplasia, and eventually lung tumors. Intraperitoneal exposure data suggest that 4-vinylphenol may be more toxic to mouse Clara cells than styrene or styrene oxide (Cruzan et al. 2005). Several species differences account for the increased sensitivity of mice, compared to rats and likely humans. Humans appear to have a lower capacity to metabolize styrene in the lung compared to rats and a much lower capacity compared to mice; additionally, humans and rats have fewer Clara cells than mice. Mouse Clara cells metabolize higher levels of styrene than rat Clara cells; likely due to the higher levels of CYP2E1 and CYP2F2 found in mice (Cruzan et al. 2002). Mice produce a higher proportion of R-styrene oxide than S-styrene oxide, as compared to rats. It has been estimated that mice produce 15 times more R-styrene oxide than rats; in humans, the S enantiomer also predominates. This is particularly important since R-styrene oxide is a more potent pneumotoxicant than S-styrene oxide. In mice and rats, a portion of the styrene oxide generated is metabolized via glutathione conjugation. Mice appear to be more susceptible to glutathione depletion than rats, and glutathione depletion has been observed in mouse lung tissue at exposure concentrations of 80–300 ppm.

Currently, the available data do not suggest that the nongenotoxic mode of action is not relevant to humans; a genotoxic mode of action have not been excluded for humans, and styrene is considered a possible human carcinogen by IARC (2002).

3.5.3 Animal-to-Human Extrapolations

Species differences exist in the metabolism of styrene in humans, rats, and mice; these differences are discussed in greater detail in Section 3.4.3. Although all three species predominantly metabolize styrene to styrene 7,8-oxide, there are species differences in the subsequent metabolism of styrene 7,8-oxide. As discussed in the metabolism section, styrene 7,8-oxide is primarily hydrolyzed to mandelic acid via epoxide hydrolase in humans. In rats and mice, styrene 7,8-oxide is also conjugated to form mercapturic

acids and styrene is metabolized to phenylacetic acid and/or 4-vinylphenol. In rats, 68–72% of the styrene metabolites in urine are generated from the epoxide hydrolase pathway and 26–35% are from the glutathione transferase pathway; in mice, 48–59 and 20–35% arise from the epoxide hydrolase and glutathione transferase pathways, respectively (Cruzan et al. 2002). In contrast, 95–100% of the styrene 7,8-oxide is metabolized via the epoxide hydrolase pathway; only trace amounts of mercapturic acids have been detected in human urine. The difference in metabolism could result in significant increases in styrene 7,8-oxide levels in the body following exposure to high levels of styrene which may result in depletion of glutathione. Additionally, a small percentage of styrene can under ring oxidation resulting in the formation of 4-vinylphenol. Ring-opened compounds account for 4–8% of the urinary metabolites in mice, less than 1% in rats, and were not detected in humans. The production of 4-vinylphenol is potentially significant mode of action because it is considered to be more toxic to the liver and lung than styrene or styrene oxide (Cruzan et al. 2005b).

However, these differences in the hepatic metabolism of styrene do not account for all of the observed species differences in styrene toxicity. As discussed in Section 3.2, mice appear to be especially sensitive to styrene toxicity in the liver, nasal olfactory, and lung. In the respiratory tract, the species differences between rats and mice are due to local metabolism of styrene to R-styrene oxide and/or other oxidized metabolites. The higher rate of metabolism in mice and higher production of the more reactive enantiomer likely result in increased susceptibility. The fact that humans have a more limited ability to metabolize styrene in the respiratory tract and possibly a higher potential to detoxify styrene oxide suggests that mice are not a good model for end points in which styrene oxide is the causative agent.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by (Thomas and Colborn 1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types

of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No *in vitro* studies were located regarding endocrine disruption of styrene.

There is some evidence in styrene workers and in female rats that inhalation exposure to styrene may disrupt the tuberoinfundibular dopaminergic system. Significant alterations in serum prolactin levels have been observed in male and female workers exposed to air concentrations as low as 50 ppm (Bergamaschi et al. 1996, 1997; Luderer et al. 2004; Mutti et al. 1984b); a regression model predicts that exposure to ≥20 ppm would result in significant elevations in serum prolactin levels (Luderer et al. 2004). Elevated serum prolactin levels have also been observed in female rats acutely exposed to 150 ppm (Umemura et al. 2005); alterations have not been observed in male rats exposed to concentrations as high as 1,500 ppm (Jarry et al. 2002; Umemura et al. 2005). As noted by NTP (2006), the clinical significance of the increased serum prolactin levels, in the absence of other reproductive effects, is not known. Styrene exposure does not appear to adversely affect thyroid stimulating hormone levels in humans (Arfini et al. 1987) or rats (Umemura et al. 2005) or follicle stimulating hormone or luteinizing hormone in humans (Arfini et al. 1987).

No significant alterations were observed in a gonadal sex differentiation assay using genetic male frogs exposed to styrene (Ohtani et al. 2001).

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

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

particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

No studies were identified that examined the toxicity of styrene in children. Several occupational exposure studies have examined the developmental toxicity of styrene; these studies did not find statistically significant alterations in the occurrence of stillbirths, infant deaths, malformations, or birth weight (Ahlborg et al. 1987; Härkönen et al. 1984; Lemasters et al. 1989). However, an expert panel (NTP 2006) evaluating these data concluded that the human studies were not sufficient to evaluate developmental toxicity due to the low statistical power of the studies and the lack of adequate information on exposure.

In general, animal studies have not found styrene-related developmental effects following inhalation exposure in rats (Murray et al. 1978), mice (Kankaanpää et al. 1980), rabbits (Murray et al. 1978), or hamsters (Kankaanpää et al. 1980) or oral exposure in rats (Daston et al. 1991; Murray et al. 1978); additionally, no developmental effects were observed in a rat two-generation study (Cruzan et al. 2005b). An expert panel determined that there was sufficient animal data to conclude that styrene does not cause developmental toxicity in rats following inhalation or oral exposure or in rabbits following inhalation exposure. No studies examined styrene toxicity following exposure of young laboratory animals.

Studies in adults, particularly reinforced plastics industry workers, have identified the nervous system as the most sensitive target of styrene toxicity. Inconsistent results have been found in animal neurodevelopmental toxicity studies. Minor alterations in forelimb grip strength and swimming ability were observed in F2 offspring of rats exposed to 500 ppm styrene; however, the investigators (Cruzan et al. 2005a) attributed these alterations to a lower body weight rather than a neurodevelopmental effect of styrene. Another inhalation study found impaired righting reflex in the offspring of rats exposed to

300 ppm during gestation (Katakura et al. 2001). Similarly, impaired amphetamine-induced locomotor activity and apomorphine-induced stereotypy were observed in the offspring of rats orally administered 200 mg/kg/day styrene during gestation and lactation (Zaidi et al. 1985).

No human or animal data were located on the toxicokinetic properties of styrene in children or immature animals or possible age-related differences in the toxicokinetics of styrene. A lactational toxicokinetic model predicted that styrene can by transferred via maternal milk (Fisher et al. 1997). Subsequent sections of this chapter (Sections 3.8, 3.10, and 3.11) discuss the available information on biomarkers, interactions, and methods for reducing toxic effects. The available information is from adults and mature animals; no child-specific information was identified. It is likely that this information will also be applicable to children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. Identification of 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) may be difficult. Biomarkers of exposure to styrene 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 styrene 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 Styrene

The elimination of styrene via expired air may be used to identify exposure to styrene (Guillemin and Berode 1988; Stewart et al. 1968). Only a small percentage of unchanged styrene is expired after cessation of exposure. There are no adequate studies correlating post-exposure exhaled styrene with previous exposure levels. Assessment of occupational exposure involving measurement of unchanged styrene in urine has been reported (Dolara et al. 1984). In this study of workers, the styrene air concentrations were 3.8–14 ppm and the urinary concentrations of styrene were 0.7–4.1 µg/L. Urinary mutagenic activity was also evaluated in this study and was not a good indication of exposure to styrene. Only a small fraction of unchanged styrene is recovered in the urine. However, measurement of styrene in urine is a reliable indicator of styrene exposure if the exposure is recent (Dolara et al. 1984; Gobba et al. 1993; Guillemin and Berode 1988; Pezzagno et al. 1985).

Analysis of unchanged styrene in blood may be used as a qualitative indicator of styrene exposure (Antoine et al. 1986). In one study, styrene was detected in the blood of humans exposed to 80 ppm (Ramsey et al. 1980). The maximum blood concentration at the end of exposure was 0.92 ± 0.26 µg/mL. The half-life values for rapid and slow clearance curves were 0.58 and 13 hours, respectively. In another study, the concentration of styrene in blood (0.2–3.7 mg/L) increased with the level and duration of styrene exposure (Baselt 1988a).

The presence of styrene in adipose tissue is also an indicator of exposure. The concentration of styrene in the adipose tissue of two workers exposed to 7.5–20 ppm of styrene during a work week suggested a half-life of 5.2 days for one worker and 2.8 days for the other worker. The elimination time was estimated to be 5 weeks (Engstrom et al. 1978b).

Levels of occupational exposure to styrene may also be estimated by measurement of styrene metabolites such as MA and PGA in urine (Bartolucci et al. 1986; Elia et al. 1980; Engstrom et al. 1976; Sedivec et al. 1984; Sollenberg et al. 1988). However, large intra-individual differences in MA and PGA urinary concentrations have been reported. A study of the inter- and intra-individual differences found that PGA levels were less variable than MA levels (Symanski et al. 2001) and variability was higher in post-shift urine samples compared to pre-shift urine samples. Expressing MA and PGA levels in units of mg per gram creatinine decreased the source intra-individual variability. Some studies found a good correlation between the time-weighted styrene exposure and urinary MA concentrations (Chua et al. 1993; Engstrom et al. 1976; Härkönen et al. 1974), while other studies found a better correlation with the sum of urinary MA and PGA at the end of the work period (Elia et al. 1980; Ong et al. 1994; Sollenberg et al. 1988). A good correlation between environmental styrene levels and urinary PGA levels has also been found (Chua et al. 1993). Total MA and PGA measured the morning after exposure may be a more reliable biological indicator of styrene exposure in factories where there is high variability in the environmental styrene concentration (Bartolucci et al. 1986).

Reference levels of styrene urinary metabolites likely to be observed in workers exposed to the time-weighted average concentrations by inhalation have been reported. The American Conference of Governmental Industrial Hygienists (ACGIH 2008) recommends a biological exposure index of 400 mg/g creatinine for the sum of MA and PGA in urine.

3.8.2 Biomarkers Used to Characterize Effects Caused by Styrene

The nervous system is the most sensitive target of styrene toxicity in humans. Styrene affects both sensory (color vision, hearing, vestibular) and motor (nerve conduction velocity) function. Impaired performance on neurobehavioral tests and diminished color vision may be indicative of styrene exposure; however, these effects are not specific to styrene and have been observed following exposure to other solvents such as toluene. Several studies have found significant associations between performance on tests of color discrimination (Eguchi et al. 1995; Kishi et al. 2001) or reaction time (Mutti et al. 1984a) and levels of styrene urinary metabolites (mandelic acid and/or phenylglyoxylic acid).

Other investigators have proposed the use of genotoxicity biomarkers. Cytogenetic monitoring of peripheral lymphocytes as a biomarker of effect has been proposed (DeJong et al. 1988; Pero et al. 1982). Future biomarkers may include hemoglobin adducts. Using unscheduled DNA synthesis (UDS) as an indicator of DNA damage, the lymphocytes of 38 individuals occupationally exposed to styrene were evaluated. The induced UDS was significantly increased for the group exposed to 1–40 ppm styrene (Pero et al. 1982). Measurement of chromosome aberration in peripheral blood lymphocyte has been used for many years to monitor the biologic effects of genotoxic chemicals. However, due to high background levels of chromosomal aberration and exposures to other genotoxic workplace chemicals, the sensitivity of this biomarker for the effects of styrene is probably not adequate (DeJong et al. 1988). The role of hepatic glutathione in the toxicity of styrene has been proposed as inhibiting the covalent binding of styrene. This has been confirmed in animal studies by decreased glutathione in styrene-exposed animals (Parkki 1978). However, its use as a biomarker of effect in humans remains to be demonstrated since data on the adverse effects of styrene on the human liver are insufficient.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Styrene metabolism is known to be inhibited by the presence of other chemicals such as toluene, trichloromethylene, and ethyl benzene. The biotransformation of styrene in rats to PGA, MA, and hippuric acid was suppressed by co-administration of toluene (Ikeda et al. 1972). This may be due to competitive inhibition of oxidative mechanisms. Similar results were reported by Ikeda and Hirayama (1978) in rats when styrene metabolism was inhibited by the administration of trichloroethylene. Urinary metabolites of styrene may be markedly reduced when humans or animals are concurrently exposed to organic solvents that inhibit styrene metabolism.

In numerous polymer industries, workers are exposed to styrene and 1,3-butadiene, and several animal studies have found that styrene affects the metabolism and toxicity of 1,3-butadiene (Laib et al. 1992; Leavens and Bond 1996; Leavens et al. 1997) and 1,3-butadiene affects the metabolism of styrene (Leavens et al. 1996); however, the affect of 1,3-butadiene on styrene toxicity has not been well examined. In other industries, workers are co-exposed to styrene and acrylonitrile; in rats receiving an intraperitoneal dose of styrene and gavage dose of acrylonitrile, increases in serum creatinine and aspartate aminotransferase levels were observed, as compared to styrene-only exposure (Normandeau et al. 1984).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Styrene is a hazardous substance found in the workplace with much lower levels found in the environment. Therefore, the populations at risk are workers in industries making polystyrene plastics, coating, polyester resins, and other products. Although no populations of unusually susceptible individuals have been identified for styrene, based on the targets of styrene toxicity, an assumption can be made that persons with pre-existing respiratory or neurological problems would be at risk for the irritant action and central nervous system effects of styrene, respectively.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to styrene. 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 styrene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to styrene:

Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: The C.V. Mosby Company, 221-222.

Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier, 956-959.

Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1226-1228.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to styrene may occur by inhalation, ingestion, or dermal contact. General recommendations for reducing absorption of styrene following exposure include removing the exposed

individual from the contaminated area and removing the contaminated clothing. If the eyes and skin were exposed, they should be flushed with water. Since aspiration of styrene into the lung can cause pulmonary edema and hemorrhage, some authors advise against the use of emetics, but recommend administration of water for dilution of gastric lavage (Bronstein and Currance 1988; Haddad and Winchester 1990). Following acute inhalation exposure, administration of oxygen and use of mechanical ventilation to support respiration have been suggested (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Administration of aminophylline and inhaled bronchodilators may be required to treat bronchospasm (Ellenhorn and Barceloux 1988). Furthermore, cardiac monitoring has been suggested. Supportive treatment may be needed for neurological effects of styrene exposure (Haddad and Winchester 1990).

3.11.2 Reducing Body Burden

Styrene is metabolized by the body, and most styrene that is absorbed is excreted in the urine as metabolites of the parent compound. Styrene is cleared rapidly from the human body. Its half-life is several hours in the blood and about 2–4 days in subcutaneous adipose tissue (see Section 3.4). No method is commonly used to enhance the elimination of the absorbed dose of styrene.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

In humans, central nervous system depression and upper respiratory tract irritation were reported following acute exposure to higher styrene concentrations (see Section 3.2). Studies in animals indicate that chronic styrene exposure causes liver and kidney effects and may induce cancer. Styrene oxide was found to be the active mutagenic metabolite of styrene in several studies (de Raat 1978; Donner et al. 1979; Norppa et al. 1979, 1980a, 1980b, 1981, 1984, 1988; Pohlova et al. 1985; Vainio et al. 1976). Based on these studies, it can be concluded that styrene is a typical indirect mutagen that needs metabolic activation to be able to bind covalently to macromolecules (e.g., nucleic acids). In one of the possible metabolic pathways, styrene oxide is further metabolized to hydroxyphenylethyl mercapturic acid. The reaction utilizes glutathione (Bond 1989). The mutagenic activity of styrene oxide was decreased in the presence of glutathione in *S. typhimurium* TA100 (Yoshikawa et al. 1980). This experiment, therefore, suggests that glutathione may reduce the mutagenic effects of styrene oxide.

The formation of styrene oxide may also contribute to other effects following styrene exposure. Glutathione decreases the cytotoxicity of many reactive chemicals by acting as a scavenger of toxic metabolites. Exposure of rodents to high levels of styrene caused depletion of glutathione content in the

liver cells of these animals (Das et al. 1983; Vainio et al. 1979). Glutathione has been suggested to decrease the hepatotoxicity by preventing styrene oxide reaction with other endogenous macromolecules. Similarly, depletion of glutathione was found in all regions of rat brain following exposure to styrene oxide (Dixit et al. 1982; Trenga et al. 1991). The authors speculated that the depletion of brain glutathione may lead to an increased concentration of free styrene oxide with increased binding to cellular nucleophiles. This process would contribute to oxidative injury to neuronal and glial cells and may be a part of styrene-induced neurotoxicity. However, that styrene itself, being a lipophilic compound, may disrupt the nerve membrane function in a manner similar to anesthetic agents.

Although results from *in vitro* studies in bacteria and *in vivo* animal studies demonstrate that exogenous glutathione precursors may decrease the effects of styrene toxicity, the benefit of this treatment is not known in humans. For low-level exposure cases, the endogenous glutathione levels are not likely to be decreased to a significant extent. Therefore, exogenous glutathione precursors such as N-acetylcysteine are not likely to be effective in mitigating the toxic effects of styrene. Exogenous doses of reducing agents may be useful following acute high dose exposure to styrene. In this case, a significant depletion of glutathione may occur as a result of the presence of high levels of styrene oxide. However, there are no clinical data available to date that support the use of this treatment.

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

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 Styrene

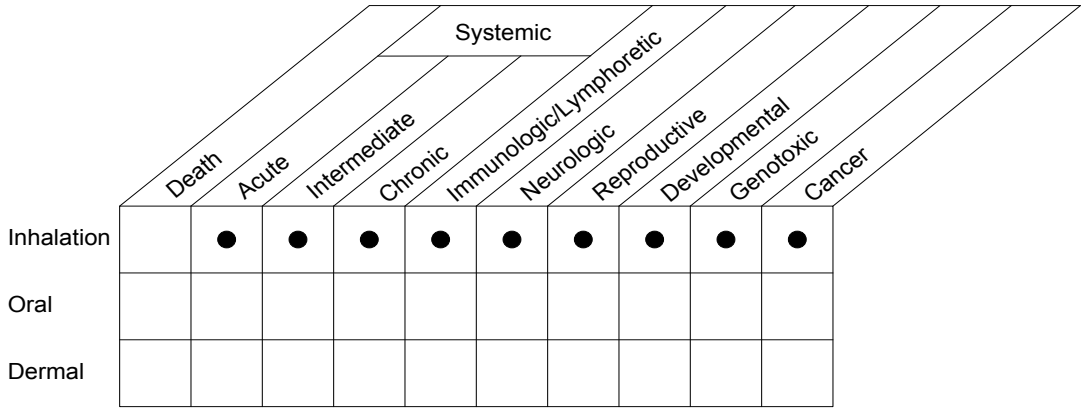
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to styrene are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of styrene. Each dot in the figure indicates that one or more 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.

There is information on most categories of human toxicity via the inhalation route from occupational studies. However, there are limited data on humans exposed to styrene by the oral or dermal routes. Data from animal studies are more extensive, with studies available for most areas of toxicity resulting from exposure via the oral and inhalation routes. Little is known about the effects of dermal exposure to styrene in animals.

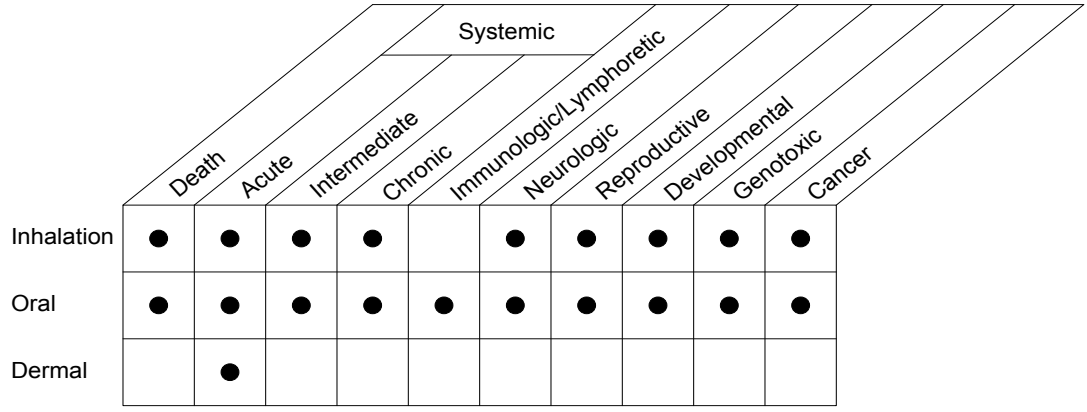
3.12.2 Identification of Data Needs

Acute-Duration Exposure. The possibility for brief human exposure to high concentrations of styrene exists in occupational settings, and might also exist near major spills. Exposure of the general public to episodic high concentrations of styrene at hazardous waste sites, in the home, or in the general environment is unlikely. The respiratory tract and central nervous system are the likely target organ systems for inhaled styrene (Alarie 1973; Carpenter et al. 1944; DeCeaurriz et al. 1983; Kankaanpää et al. 1980; Murray et al. 1978; Seeber et al. 2004; Spencer et al. 1942; Stewart et al. 1968). Animal studies have reported hepatic (Cruzan et al. 1997, 2001; Morgan et al. 1993a, 1993b, 1993c; Vainio et al. 1979) and nasal (Cruzan et al. 2001) effects and hearing impairments (Campo et al. 2001; Crofton et al. 1994; Lataye et al. 2003). Available toxicokinetic data suggest that the mouse may be more sensitive to the hepatic and nasal toxicity of styrene than humans; thus, these data are not suitable for derivation of an acute-duration inhalation MRL. Studies have also examined potential reproductive (Salomaa et al. 1985) and developmental (Kankaanpää et al. 1980; Murray et al. 1978) effects; the highest doses tested in these studies were NOAELs. An acute-duration inhalation MRL based on a NOAEL for neurological effects in humans (Ska et al. 2003) was derived. Episodic high-level exposures to styrene from contaminated food

Figure 3-6. Existing Information on Health Effects of Styrene



Human



Animal

● Existing Studies

or water are unlikely. Few studies have examined the toxicity of styrene following exposure to an acute oral dose. Abdominal discomfort was observed in residents exposed to elevated levels of styrene in drinking water (Arnedo-Pena et al. 2003); concomitant inhalation exposure to styrene limits the utilization of this study for MRL derivation. A study in rats identified a LOAEL for neurotoxicity (Husain et al. 1985) and another rat study examined potential developmental effects, but found no adverse effects (Daston et al. 1991). An acute-duration oral MRL was derived using the neurotoxicity study conducted by Husain et al. (1985). Although data on the toxicity of styrene following acute inhalation or oral exposure were considered adequate for the derivation of MRLs, the databases are limited to a few studies; additional studies confirming the dose-response relationships would increase the confidence in these MRLs. Dermal exposure to styrene at significant levels is unlikely except in the case of workplace spills and dermal absorption is probably low based on limited human studies. However, the almost complete lack of dermal toxicity data in animals and humans creates a degree of uncertainty on this issue. Therefore, single-dose dermal studies would be useful in determining target organs and thresholds for dermal exposure. In designing these types of studies, precautions should be taken to avoid concomitant inhalation exposure.

Intermediate-Duration Exposure. Information on the toxicity of styrene in humans following intermediate-duration inhalation exposure is limited to a study examining potential reproductive effects in workers (Lindbohm et al. 1985); however, exposure information was not provided. Inhalation studies in animals have reported damage to the nasal olfactory epithelium in rats (Cruzan et al. 1997, 2005a, 2005b; Ohashi et al. 1986) and mice (Cruzan et al. 1997, 2001), liver damage in mice (Cruzan et al. 1997), eye irritation in rats (Cruzan et al. 1997) and guinea pigs (Spencer et al. 1942), ototoxicity in rats (Campo et al. 2001; Lataye et al. 2000; Loquet et al. 1999, 2000; Makitie et al. 2002; Pouyatos et al. 2002; Pryor et al. 1987; Yano et al. 1992), and impaired nerve conduction velocity (Yamamoto et al. 1997). A two-generation study in rats did not find reproductive, developmental, or neurodevelopmental effects (Cruzan et al. 2005a, 2005b), but another study did find neurodevelopmental effects (Katakura et al. 1999, 2001). However, additional studies are needed, as the data are not considered sufficient to derive an intermediate-duration inhalation MRL. Chronic exposure studies provide strong evidence that the nervous system is the most sensitive target of styrene toxicity; studies examining neurological function of workers exposed to styrene for <1 year would provide valuable data for deriving an intermediate-duration inhalation MRL. Oral exposure studies of intermediate-duration are limited to a small number of animal studies and no human data; observed effects include impaired learning in rats (Bushnell 1994) and decreases in spermatozoa in rats (Srivastava et al. 1989, 1992a, 1992b). The results of the Srivastava studies have been questioned by the NTP Expert Panel (NTP 2006) because the findings are inconsistent

with the lack of reproductive effects found in an inhalation two-generation study conducted by Cruzan et al. (2005b). The LOAELs identified in these studies were higher than the lowest LOAEL identified in an acute-duration neurotoxicity study (Husain et al. 1985). The intermediate-duration database was considered inadequate for derivation of an MRL because an intermediate-duration oral MRL based on the LOAELs identified in the intermediate-duration oral studies would be higher than the acute-duration oral MRL. Studies in animals are needed to establish dose-response relationships for neurotoxicity, the presumed sensitive end point. Additionally, more studies examining the potential reproductive toxicity of ingested styrene are needed to confirm the results of the Srivastava studies. One study examined the dermal toxicity of styrene in rabbits (Spencer et al. 1942); basic information on the adverse effects of intermediate-duration dermal exposure to styrene in animals is also needed due to the sparsity of available data.

Chronic-Duration Exposure and Cancer. A large number of occupational exposure studies have examined the chronic toxicity of styrene. Systemic toxicity studies have examined endocrine (Bergamaschi et al. 1997; Mutti et al. 1984b), hematological (Checkoway and Williams 1982; Thiess and Friedheim 1978), hepatic (Hotz et al. 1980; Lorimer et al. 1978), or renal (Verplanke and Herber 1998; Viau et al. 1987; Vyskocil et al. 1989) end points; most studies relied on biomarkers of toxicity. The most widely examined end point is neurotoxicity and the available data suggest that this is the most sensitive end point. Examined neurological end points included color vision (Campagna et al. 1995, 1996; Chia et al. 1994; Eguchi et al. 1995; Fallas et al. 1992; Gobba et al. 1991; Gong et al. 2002; Kishi et al. 2001; Mutti et al. 1984a), vestibular effects (Calabrese et al. 1996; Möller et al. 1990), hearing impairment (Morata et al. 2002; Morioka et al. 1999; Muijser et al. 1988; Śliwińska-Kowalska et al. 2003), symptoms of neurotoxicity (Checkoway et al. 1992; Cherry et al. 1980; Edling et al. 1993; Viaene et al. 1998, 2001), performance on neurobehavioral tests (Cherry et al. 1980; Edling et al. 1993; Gamberale et al. 1976; Jegaden et al. 1993; Lindstrom et al. 1976; Mutti et al. 1984a; Tsai and Chen 1996; Viaene et al. 1998, 2001), nerve conduction velocity (Behari et al. 1986; Murata et al. 1991; Rosen et al. 1978), olfactory alterations (Dalton et al. 2003, 2007), and EEG alterations (Härkönen et al. 1984; Seppäläinen and Härkönen 1976). Other human studies have examined reproductive (Härkönen and Holmberg 1982; Hemminki et al. 1980) and developmental (Ahlborg et al. 1987; Lemasters et al. 1989) end points. The chronic toxicity of styrene has also been examined in rat (Cruzan et al. 1998; Jersey et al. 1978) and mouse (Cruzan et al. 2001) studies. The occupational exposure studies were considered adequate for derivation of a chronic-duration inhalation MRL for styrene. Further research to define the dose-response curve more fully and to identify a chronic inhalation NOAEL for neurological effects would be valuable and would help to reduce uncertainty in the MRL. Data on chronic oral exposure to

styrene is only available through animal studies (Beliles et al. 1985; Conti et al. 1988; NCI 1979b; Quast et al. 1979). In these studies, the most sensitive indicator of toxicity appears to be Heinz body formation in red blood cells in dogs (Quast et al. 1979) and the EPA has calculated a chronic oral RfD based on this study (IRIS 2009). However, there is some doubt regarding the chronic oral NOAEL, and whether hematological effects are really more sensitive than neurological effects. Moreover, decreased survival has been noted in rats at exposure levels only slightly higher than the no-effect level for hematological effects (Conti et al. 1988). Therefore, no chronic oral MRL has been derived. Further studies on the effects of oral exposure, with special emphasis on neurological or neurobehavioral effects, would be valuable. Although chronic dermal exposure by the general public is not likely, there may be some potential for dermal contact with soil at hazardous waste sites. Therefore, data on long-term effects of dermal contact with styrene would be useful.

Taken together, the animal and human data indicate that styrene may possibly be a weak human carcinogen. Although data from epidemiological studies are limited due to concurrent chemical exposures and small cohorts, the data are suggestive of some carcinogenic potential in humans (Antilla et al. 1998; Bond et al. 1992; Cheng et al. 2007; Coggon et al. 1987; Delzell et al. 1996, 2001; Frentzel-Beyme et al. 1978; Gerin et al. 1998; Graff et al. 2005; Hodgson and Jones 1985; Kogevinas et al. 1993, 1994; Kolstad et al. 1993, 1994, 1995; Macaluso et al. 1996; Matanoski and Schwartz 1987; Matanoski et al. 1990; McMichael et al. 1976; Meinhardt et al. 1982; Nicholson et al. 1978; Okun et al. 1985; Ott et al. 1980; Sathiakumar et al. 2005; Wong 1990; Wong et al. 1994). Inhalation and oral exposure studies in rats have not found significant increases in the incidence of neoplastic tumors (Beliles et al. 1985; Conti et al. 1988; Cruzan et al. 1998; Jersey et al. 1978; Maltoni et al. 1979; NCI 1979b). However, inhalation and oral studies in mice have found significant increases in the incidence of neoplastic lung tumors (Cruzan et al. 2001; NCI 1979b). The available data suggest that toxicokinetic differences between rats, mice, and humans result in an increased sensitivity of mice. Clarification of the data is needed in several areas. Almost all of the available epidemiological studies involve concurrent exposures to other chemicals. The role of the metabolism of styrene in humans and animals needs to be clarified and the carcinogenic mechanisms needed to be further elucidated. Additional studies that account for these issues would be valuable.

Genotoxicity. The results of genotoxicity tests for styrene both *in vivo* and *in vitro* are frequently conflicting, and the genotoxic potential of styrene is not clear (Andersson et al. 1980; Beliles et al. 1985; Hogstedt et al. 1979; Meretoja et al. 1977, 1978; Watanabe et al. 1981). The reasons for the mixed or conflicting genotoxicity results may be differences in the metabolism or detoxification of styrene in the

various test systems employed. The role of the metabolite styrene oxide in genotoxicity assays on styrene should be fully evaluated, preferably in mammalian *in vivo* systems. Toxicokinetic studies evaluating the presence, level, and activity of styrene oxide in humans will influence the interpretation of genotoxicity studies on styrene and their relevance to public health.

Reproductive Toxicity. Occupational exposure studies have examined male and female styrene workers to evaluate potential reproductive effects; however, most of these studies did not quantify styrene exposure or exposure to other compounds, thus, interpretation of results is difficult. Inconsistent results have been reported for spontaneous abortions with some studies reporting significant increases (Härkönen and Holmberg 1982; Hemminki et al. 1980; McDonald et al. 1988) and others reporting no effect (Härkönen and Holmberg 1982; Hemminki et al. 1980, 1984; Lindbohm et al. 1985). Oligomenorrhea was observed in one study of workers (Cho et al. 2001), but not in another study (Lemasters et al. 1985). Studies in male workers have found alterations in sperm parameters (Kolstad et al. 1999a), but no alterations in time-to-pregnancy (Kolstad et al. 2000; Sallmén et al. 1998) or fertility rates (Kolstad et al. 1999c). A two-generation inhalation study (Cruzan et al. 2005b) and three-generation oral study (Beliles et al. 1985) in rats showed no styrene-related reproductive effects. However, testicular effects have been observed in an oral exposure study (Srivastava et al. 1989), but not in two inhalation studies (Cruzan et al. 2005b; Salomaa et al. 1985). Additional reproductive data on occupationally-exposed males would be useful in evaluating the existing animal data that indicates altered testicular function and studies in females would be useful in evaluating the inconsistent findings in the existing studies.

Developmental Toxicity. Data on the developmental effects of inhalation exposure to styrene are available in humans and animals. Occupational exposure studies (Ahlborg et al. 1987; Härkönen et al. 1984; Lemasters et al. 1989) have not found increases in the occurrence of birth defects or decreases in birth weight. However, interpretation of the results are complicated by exposure to other chemicals and lack of information on exposure levels. Additional occupational studies are needed to adequately assess this end point. Developmental studies in animals via inhalation (Cruzan et al. 2005b; Kankaanpää et al. 1980; Murray et al. 1978) or oral (Beliles et al. 1985) exposure have not found effects on fetal outcome, birth weight, or incidence of abnormalities. However, several studies have reported neurodevelopmental (Katakura et al. 1999, 2001; Zaidi et al. 1985) or reproductive (Srivastava et al. 1992a, 1992b) effects. Additional studies are needed to examine the potential effects on the nervous and reproductive systems of developing organisms. No studies examined the developmental toxicity of styrene following dermal exposure.

Immunotoxicity. Occupational exposure studies have found alterations in lymphocyte subsets (Bergamaschi et al. 1995b; Biró et al. 2002), which may be indicative of reduced cell-mediated immunity and an impaired immune response to concanavalin (Tulinska et al. 2000). Limited data in animals indicate that inhalation (Ban et al. 2006) and oral (Sinitskij discussed in WHO 1983) exposure can also result in impaired immune response. No dermal exposure studies examining immunotoxicity were identified. Human and animal studies provide suggestive evidence that the immune system is a target; additional studies would be useful to further investigate the effect of styrene on immune function.

Neurotoxicity. The neurotoxicity of styrene in workers in the reinforced plastic industry has been extensively examined (Behari et al. 1986; Calabrese et al. 1996; Campagna et al. 1995, 1996; Castillo et al. 2001; Checkoway et al. 1992; Cherry et al. 1980; Chia et al. 1994; Dalton et al. 2003; Edling et al. 1993; Eguchi et al. 1995; Fallas et al. 1992; Fung and Clark 1999; Gamberale et al. 1976; Gobba et al. 1991, 1995; Gong et al. 2002; Härkönen et al. 1984; Iregren et al. 2005; Jegaden et al. 1993; Kishi et al. 2001; Lindstrom et al. 1976; Matikainen et al. 1993a, 1993b; Möller et al. 1990; Morata et al. 2002; Morioka et al. 1999; Muijser et al. 1988; Murata et al. 1991; Mutti et al. 1984a; Niklasson et al. 1993; Rosen et al. 1978; Seppäläinen and Härkönen 1976; Śliwińska-Kowalska et al. 2003; Štětkářová et al. 1993; Triebig et al. 1985, 2001; Tsai and Chen 1996; Viaene et al. 1998, 2001; Yuasa et al. 1996). A variety of neurological effects have been observed in these studies including decreased color discrimination, slowed reaction time, altered performance on neurobehavioral tests of memory and learning, altered vestibular function, altered hearing, reduced nerve conduction velocity, and increased clinical symptoms such as dizziness, tiredness, memory loss, and feeling drunk. Additionally, several experimental studies have examined the effects of acute exposure on vestibular function (Ödkvist et al. 1982; Stewart et al. 1968), clinical symptoms (Seeber et al. 2004; Ska et al. 2003; Stewart et al. 1968), color discrimination (Ska et al. 2003), and performance on neurobehavioral tests (Seeber et al. 2004; Ska et al. 2003). Animal studies have primarily focused on the damage to the organ of Corti and hearing loss (Campo et al. 2001; Crofton et al. 1994; Lataye et al. 2003; Loquet et al. 1999, 2000; Makitie et al. 2002; Pouyatos et al. 2002; Pryor et al. 1987; Yano et al. 1992), although nerve conduction velocity has also been examined (Kulig 1988; Yamamoto et al. 1997). The potential for neurotoxicity has not been examined in humans orally exposed to styrene and a limited number of end points have been examined in animals (Agrawal et al. 1982; Bushnell 1994; Husain et al. 1980, 1985; Khanna et al. 1994). The neurological effects observed in styrene workers were used as the basis of a chronic-duration inhalation MRL. Since this is based on a LOAEL, further studies which define the chronic NOAEL, as well as acute- and intermediate-duration NOAELs, would be valuable especially at levels of styrene causing problems with coordination and psychological function. These and other neurological effects may play a

role in the rate of workplace accidents and the level of performance. Additional studies in mammalian animal models are needed to determine if styrene causes chronic damage to the central and/or peripheral nervous systems and to determine the associated mechanism of toxicity. Also, information is needed to determine if neurotoxicity is a sensitive end point from exposure to styrene via the oral route.

Epidemiological and Human Dosimetry Studies. Numerous studies have examined the toxicity of styrene in workers, as discussed in other sections, most of these studies have focused on neurotoxicity and potential carcinogenicity of styrene. A common limitation of these studies is the poor characterization of exposure levels and possible exposure to other chemicals. Some studies provided no data on styrene exposure levels and other studies provide current exposure levels with limited or no data on past exposure levels. Occupational exposure and experimental studies also provide suggestive evidence of acute upper respiratory tract irritation and eye irritation (Carpenter et al. 1944; NIOSH 1983) Stewart et al. 1968) and possible endocrine effects (elevated levels of serum prolactin) (Arfini et al. 1987; Bergamaschi et al. 1996, 1997; Luderer et al. 2004; Mutti et al. 1984b); additional studies are needed to confirm the results of these studies and to establish dose-response relationships. Additionally, there are suggestive findings that styrene has the potential to induce reproductive effects (Cho et al. 2001; Härkönen and Holmberg 1982; Hemminki et al. 1980; Kolstad et al. 1999c; McDonald et al. 1988); however, poor characterization of styrene exposure, possible exposure to other compounds (particularly for the Cho et al. (2001) study), the low statistical power of the studies, and the lack of positive associations in the follow-up study (Hemminki et al. 1984) to the Hemminki et al. (1980) study limit the usefulness of the studies. Studies of males and female styrene workers examining a variety of reproductive end points and adequately characterized exposure would be useful.

Biomarkers of Exposure and Effect.

Exposure. Available studies indicate that there are good quantitative relationships between styrene metabolites (MA and PGA) in the urine and styrene exposure levels in humans (Bartolucci et al. 1986; Chua et al. 1993; Elia et al. 1980; Engstrom et al. 1976; Härkönen et al. 1978; Ong et al. 1994; Sedivec et al. 1984; Sollenberg et al. 1988; Symanski et al. 2001). Levels of styrene in blood have also been used as a biomarker of exposure (Antoine et al. 1986; Baselt et al. 1988a; Ramsey et al. 1980).

Effect. There are currently no biomarkers specific for the effects of styrene that are not also typical of other central nervous system depressants. Further research is needed to evaluate potential biomarkers of effect in the areas of chromosome aberrations, psychomotor decrement, hepatic glutathione depletion, and

adipose tissue retention of styrene. These potential biomarkers should be evaluated in terms of long-term or chronic exposure periods, and their specificity for exposure to styrene.

Absorption, Distribution, Metabolism, and Excretion. Styrene oxide (styrene epoxide) has been identified as an intermediate metabolite of styrene (Drummond et al. 1989; Engstrom et al. 1976; Korn et al. 1984, 1987; Leibman 1975; Lof et al. 1983; Withey and Collins 1979; Young et al. 1979). However, styrene oxide has only been found in minute amounts in human studies (Lof et al. 1986a). The presence of styrene oxide, a mutagen and carcinogen, may account for some conflicting results and/or interspecies variation in mutagenicity tests and cancer bioassays. The role, if any, of styrene oxide in the overall toxicity of styrene needs to be evaluated by additional metabolism studies to confirm its presence, level, and duration in human tissues. The toxicokinetics of styrene exposure via inhalation are reasonably well defined. However, oral and dermal exposure data are needed to better characterize absorption rates and the elimination ratios of the metabolites (MA and PGA).

Comparative Toxicokinetics. Interspecies variations in styrene metabolism have been established. Differences in the relative proportion of urinary metabolites, which is indicative of different metabolic pathways have been found in humans, mice, and rats. Additionally, there are differences in the kinetic constants for cytochrome P450 and epoxide hydrolase, which result in higher levels of reactive metabolites in the liver, lungs, and nasal epithelium. Also, mice appear to generate a higher proportion of R-styrene oxide than S-styrene oxide; the R-enantiomer is believed to be more cytotoxic. These metabolic differences are believed to result in mice being more sensitive than rats or humans to liver, lung, and nasal toxicity. Potential species differences in the neurotoxicity, the most sensitive end point in humans, have not been examined; if the neurological effects are due to styrene rather than one of its metabolites, the observed species differences may not be relevant. Efforts should continue to identify which animal model best approximates human metabolism of styrene.

Methods for Reducing Toxic Effects. Recommended methods for the mitigation of acute effects of styrene intoxication include mechanical ventilatory support, administration of oxygen, and drug therapy for bronchospasm, if exposure is by inhalation (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988). Thorough washing or flushing with water is recommended for dermal/ocular exposure. Supportive treatment is indicated for neurological effects of styrene exposure (Haddad and Winchester 1990). No information was located concerning mitigation of effects of lower-level or longer-term exposure to styrene. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating styrene-exposed populations in

the vicinity of hazardous waste sites. This includes further studies on the mechanism(s) of styrene toxicity, so that methods may be developed to interfere with or block styrene's toxic actions in the body.

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.

No studies were identified that examined the toxicity of styrene in children or young laboratory animals. No consistently observed developmental effects have been reported in occupational exposure studies (Ahlborg et al. 1987; Härkönen et al. 1984; Lemasters et al. 1989) or in animal studies (Cruzan et al. 2005b; Daston et al. 1991; Kankaanpää et al. 1980; Murray et al. 1978). The nervous system is the most sensitive target of styrene toxicity in adults. No adverse styrene-related effects were observed in neurobehavioral function tests in rats exposed to styrene during gestation and lactation (Cruzan et al. 2005a); however, neurological effects have been observed in another inhalation study of rats exposed during gestation (Katakura et al. 2001) and in an oral gestation and lactation study (Zaidi et al. 1985). Possible neurological effects have not been assessed following post-weaning exposure; these data would be useful in evaluating whether growing children are more susceptible than adults to styrene-induced neurotoxicity.

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

No ongoing studies on styrene were identified in Federal Research in Progress database (FEDRIP 2007).

4. CHEMICAL AND PHYSICAL INFORMATION

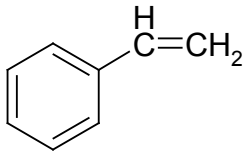
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of styrene is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-1. Chemical Identity of Styrene

Characteristic	Information	Reference
Chemical name	Styrene	Verschueren 1983
Synonym(s)	cinnamene; cinnamol; ethenylbenzene; phenylethylene; styrol; vinylbenzene;	Verschueren 1983; HSDB 2009
Registered trade name(s)	No data	
Chemical formula	C_8H_8	Windholz 1983
Chemical structure		IARC 1994
Identification numbers:		
CAS registry	100-42-5	Sax and Lewis 1987
NIOSH RTECS	WL3675000	HSDB 2009
EPA hazardous waste	No data	
EINICS	202-851-5	ESIS 2009
OHM/TADS	7216911	HSDB 2009
DOT/UN/NA/IMDG shipping	IMDG 3.3	HSDB 2009
	UN 2055	HSDB 2009
HSDB	171	HSDB 2009
NCI	C02200	HSDB 2009

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

Table 4-2. Physical and Chemical Properties of Styrene

Property	Information	Reference
Molecular weight	104.15	O'Neil et al. 2001 Lide 2005
Color	Colorless to yellowish	Windholz 1983
Physical state	Liquid	Sax and Lewis 1987
Melting point	-30.6 °C	O'Neil et al. 2001
Boiling point	145.2 °C	Verschueren 2001; Weast 1985
Density at 20 °C	0.9059	O'Neil et al. 2001
Odor	If pure, sweet and pleasant; commonly contains aldehydes which provide it with a penetrating, sharp, and unpleasant smell	Verschueren 2001
Odor threshold:		
Water	0.73 mg/L	HSDB 2009
	0.011 mg/L	Amoore and Hautala 1983
Air	1.36 mg/m^3	Amoore and Hautala 1983
Solubility:		
Water at 15 °C Water at 20 °C Water at 40 °C	280 mg/L 300 mg/L 400 mg/L	Verschueren 2001
Organic solvents	Soluble in alcohol, ether, acetone, carbon disulfide	Windholz 1983
Partition coefficients:		
Log K_{ow}	2.95	Hansch et al. 1995; EPA 1984a
Log K_{oc}	2.96	Sabljic et al. 1995
Vapor pressure at 20 °C	5 mmHg	Verschueren 2001
Henry's law constant at 25 °C	2.61x10^{-3} atm-m^3/mol (calculated)	EPA 1981
Autoignition temperature	914 °F (490 °C)	Sax and Lewis 1987
Flashpoint	87 °F (31 °C) (closed cup) 34.4°C (Tag open cup)	O'Neil et al. 2001; Kirk-Othmer 2001
Flammability limits	No data 0.9 (lower); 6.8 (higher) 1.1 (lower); 6.1 (higher)	 CEFIC 2008; Kirk-Othmer 2001
Conversion factors	1 mg/m^3=0.23 ppm; 1 ppm=4.33 mg/m^3	Verschueren 2001

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

5.1 PRODUCTION

In the United States, styrene is produced principally by the catalytic dehydrogenation of ethylbenzene. Hence, ethylbenzene is a common contaminant. Styrene is also produced by oxidation of ethylbenzene to ethylbenzene hydroperoxide, which is then reacted with propylene to produce propylene oxide and α-methylphenyl carbinol. The carbinol is then further dehydrated to produce styrene (Carlson and Erskine 1973; HSDB 2009; IARC 1979). The first route of manufacture (dehydrogenation of ethylbenzene) represents 90% of styrene production. The other described method is the second most commonly used route of styrene synthesis. Other methods of styrene production are rarely used.

Styrene has been manufactured in the United States since 1938, with production increasing dramatically over the last 30 years. Since 1977, U.S. total styrene production has more than doubled. Production increased 16% in the decade between 1977 and 1987, but production increased >32% between 1987 and 1999, and rose again by another 28% between the years 1999 and 2006 (HSDB 2009; SRI 2006). Specifically, U.S. production of styrene in 1978 was 6.8 billion pounds, and then in 1987, production was approximately 8 billion pounds (USITC 1987, 1988). In 1999, U.S. styrene production was over 10 billion pounds, and in 2006, the production capacity in the United States was >13 billion pounds (HSDB 2009; SRI 2006). The annual U.S. styrene production capacity in 2008 was 12.2 billion pounds (SRI 2008).

Information regarding the locations of the numerous styrene production facilities and the amounts of styrene that may be present on-site is presented in Table 5-1. Current domestic producers of styrene include Chevron Phillips Chemical Company LP (Aromatics and Styrenics Business Unit), St. James, Louisiana; Cos-Mar Company, Carville, Louisiana; the Dow Chemical Company, Freeport, Texas; INEOS Americas, LLC, Bayport, Texas and Texas City, Texas; LyondellBasell Industries, Channelview, Texas; and Westlake Styrene LP, Sulphur, Louisiana (SRI 2008). The production of styrene at these facilities is directed primarily for captive processes (on-site conversion to other materials) or for merchant sales to other entities (these include export). The information presented in Table 5-1 reflects the locations of these production plants, where it can be noted that the greatest production capacity occurs primarily in Texas and Louisiana.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	87	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	58	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	54	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
CA	192	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	24	100	9,999,999	2, 3, 6, 7, 8, 9, 11, 12, 13
CT	24	0	49,999,999	3, 5, 6, 7, 8, 9, 11, 12
DE	22	100	999,999	1, 2, 3, 4, 6, 7, 8, 11, 12, 14
FL	163	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	106	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GU	1	100	999	9
HI	3	100	9,999	2, 3, 6, 7, 8, 10, 11
IA	50	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
ID	16	0	99,999	1, 2, 3, 6, 7, 8, 11, 12
IL	111	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	169	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	53	0	99,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	68	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	125	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	34	0	499,999,999	2, 3, 4, 6, 7, 8, 9, 12, 13
MD	39	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
ME	17	100	99,999	2, 3, 6, 7, 8, 10, 11
MI	107	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	73	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MO	81	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MS	48	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MT	9	100	9,999,999	3, 6, 7, 8, 9, 10, 13
NC	113	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
ND	17	1,000	499,999,999	2, 3, 6, 7, 8, 9, 10, 11, 13
NE	38	0	999,999	1, 2, 3, 6, 7, 8, 10, 11, 12, 13
NH	27	100	499,999,999	2, 3, 5, 6, 7, 8, 10, 11, 12
NJ	53	100	99,999,999	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NM	19	100	49,999,999	1, 2, 3, 6, 7, 8, 9, 11, 12
NV	11	1,000	99,999,999	2, 3, 6, 7, 8, 10, 11
NY	60	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	205	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	59	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	57	100	49,999,999	1, 2, 3, 6, 7, 8, 9, 10, 11, 12
PA	127	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	29	0	9,999,999	1, 2, 3, 6, 7, 8, 10, 11, 12
RI	31	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
SC	84	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
SD	8	1,000	99,999	1, 2, 3, 6, 7, 8, 10, 11
TN	105	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	272	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	42	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	65	0	49,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12
VT	5	1,000	99,999	6, 7, 8
WA	89	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	95	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
WV	41	100	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WY	2	1,000	9,999	6, 8, 9

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

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

Source: TRI06 2008 (Data are from 2006)

5.2 IMPORT/EXPORT

Imports of styrene have generally been <1% of U.S. domestic production volumes, with imported styrene amounts decreasing over the last decades, and exported amounts increasing during the same time period. Styrene imports were reported to be 26.4 million pounds for 1976, 320 million pounds in 1986 (Carlson and Erskine 1973; IARC 1979), but only 1 million pounds in 1999 (HSDB 2009). These trends indicate a higher capacity for domestic producers to meet industry needs. Styrene exports were <1 billion pounds in 1978, but had exceeded 1 billion pounds by 1983. Exports have slowly increased such that recent export data indicate that the U.S. exports >2 billion pounds of styrene annually (HSDB 2009), also indicating that domestic production is more than capable to serve domestic needs. However, future styrene exports are forecast to drop off because of significant global oversupply, slowing economic growth, and the start-up of new styrene facilities in the Middle East (Chemical Week 2008).

5.3 USE

Styrene is used predominantly (65% of total product) in the production of polystyrene plastics and resins (James and Castor 2005). In addition, fiberglass products used for boats are also made from polyester resins dissolved in styrene. Styrene is also used as an intermediate in the synthesis of materials used for ion exchange resins and to produce copolymers such as styrene-acrylonitrile (SAN) and acrylonitrile-butadiene-styrene (ABS), both representing approximately 9% of styrene use, and styrene-butadiene rubber (SBR), representing approximately 6% of styrene use. SBR is used for such products as car tires, hoses used for industrial applications, and shoes. A related polymer, styrene-butadiene latex (approximately 7%), is used in making carpet, coatings for paper, and as part of latex paints. SAN and ABS are used for materials such as piping, automotive components, refrigerator liners, plastic drinking glasses, and car battery enclosures. An additional 7% of styrene is formulated with unsaturated polyester resins in such things as boat hulls (fiberglass reinforcement materials). The remaining amounts of styrene produced are used for several types of applications, including less common thermoplastics and even for laboratory and water purification uses (ion-exchange resins) and glues and adhesives (James and Castor 2005). Styrene copolymers are also frequently used in liquid toner for photocopiers and printers (HSDB 2009).

The Food and Drug Administration (FDA) permits styrene to be used as a direct additive for synthetic flavoring and an indirect additive in polyester resins, ion-exchange membranes, and in rubber articles (5% by weight maximum) intended for use with foods (HSDB 2009; IARC 1979; NIOSH 1983).

5.4 DISPOSAL

Typical means of styrene disposal include absorption on vermiculite or similar material, followed by disposal in an EPA-permitted landfill. Incineration is also a useful disposal method, but this must be carefully controlled since pure styrene is highly flammable (HSDB 2009). No data were located regarding the quantities of styrene disposed by these means on a national level, but the state of Massachusetts reported that most styrene disposal occurred via incineration (95.5%), followed by smaller amounts being disposed of in landfills (0.5%), a slightly greater amount being subjected to solvent recovery (0.7%), and slightly more being transferred to waste/energy brokers (3.3%) (Keenan and Harriman 1993). The total amounts represented were ~250,000 pounds. Whether the data reported for Massachusetts are representative of the proportions disposed of by these means in other states is not known.

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Styrene has been identified in at least 251 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 styrene is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 30 are located within the United States and one is located in the Commonwealth of Puerto Rico (not shown).

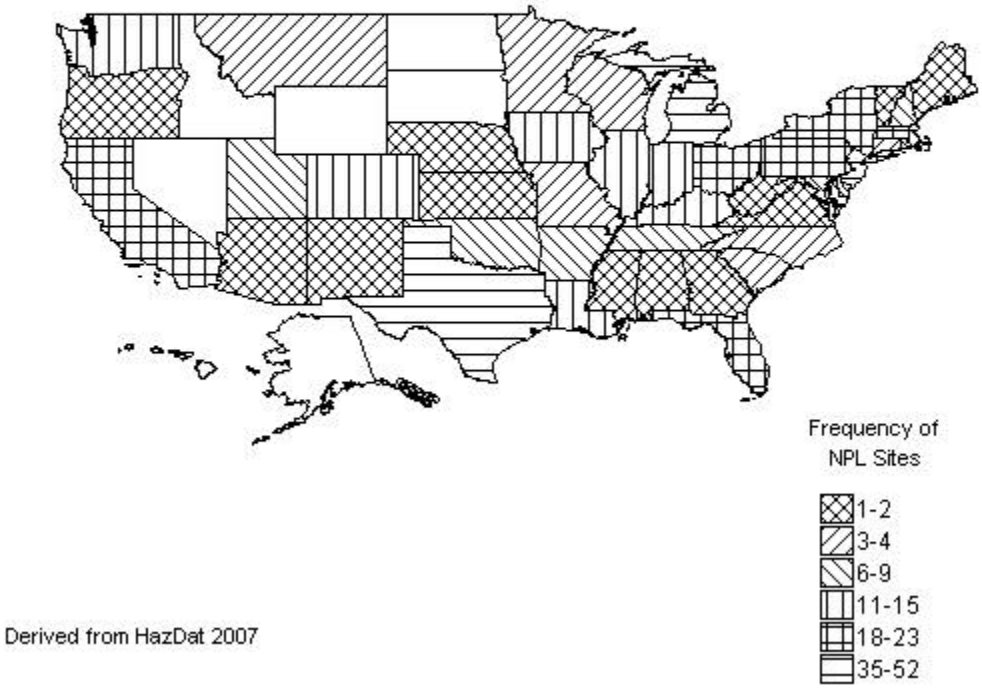
Styrene is a widely used industrial chemical with reported atmospheric emissions of >51 million pounds annually in the United States (TRI06 2008). Styrene photodegrades in the atmosphere, with a half-life ranging between 7 and 16 hours (which are the degradation half-lives catalyzed by reactions with hydroxyl radical and ozone, respectively). Styrene is moderately mobile in soil and volatilizes from water to the atmosphere. Styrene will undergo biodegradation in most top soils and aquatic environments, but degradation will be much slower in environments that are anaerobic. Bioconcentration does not appear to be significant.

The principal route of styrene exposure for the general population is probably by inhalation of contaminated indoor air. Mean indoor air levels of styrene have been reported in the range of 0.1–50 $\mu g/m^3$, and can be attributed to emissions from building materials, consumer products, and tobacco smoke. It should be pointed out that the workplace or home office may have substantially higher levels of airborne styrene, due to emissions from laser printers and photocopiers. General workplace styrene concentrations ranged from 89 to $1.5x10^6$ $\mu g/m^3$ (20–$3.4x10^5$ ppmv). The most significant exposure route in these settings is also likely by inhalation. The industries with the highest potential exposure are probably the reinforced plastics factories, boatbuilding facilities, and polystyrene factories. Exposure may also be high in areas near major spills. Exposure to styrene from hazardous waste sites is potentially important, but the magnitude of the problem is unknown. The potential for outdoor exposure to styrene is lower than indoor exposure, with reported mean air levels ranging from 0.28 to 20 $\mu g/m^3$ (0.064–4.6 ppmv).

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

Figure 6-1. Frequency of NPL Sites with Styrene Contamination



facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 47.3 million pounds (21,500 metric tons) of styrene to the atmosphere from 1,558 domestic manufacturing and processing facilities in 2006, accounted for 93% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Table 6-1.

Styrene may be emitted to the atmosphere from industrial production and usage processes, motor vehicle operation, combustion processes, building materials, and consumer products. Estimated atmospheric industrial styrene emissions reported to EPA for the 2005 TRI totaled 47.3 million pounds, with >38 million pounds released from point sources and >10 million pounds released as fugitive emissions (TRI06 2008). Styrene ranked 16th among air emissions for reported chemicals and chemical group compounds in the United States in 2005. Since EPA regulations that require reporting of toxic chemical emissions apply only to selected facilities producing and/or using substantial quantities of the chemical (EPA 1988a), the total air emissions of styrene are probably greater than those reported. Typical sources of industrial styrene emissions are those facilities producing styrene, polystyrene, other plastics, synthetic rubber, and resins (EPA 1975, 1987d; Graedel 1978; IARC 1979; NIOSH 1983). The number of facilities reporting styrene emissions to the TRI are listed in Table 6-1, along with number of reporting facilities in each state and Puerto Rico, and the primary routes of styrene release from those facilities.

Styrene has been identified as a component of motor vehicle emissions from both gasoline- and diesel-powered engines (Hampton et al. 1982, 1983). Styrene emission rates ranging from 6.2 to 7.0 mg/km

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	37	1,493,262	501	0	4,259	0	1,493,763	4,259	1,498,021
AR	27	656,082	0	0	32,770	1,455	656,082	34,225	690,307
AZ	23	555,904	1,458	0	63,937	0	557,362	63,937	621,299
CA	104	2,185,575	115	0	7,042	2,316	2,186,674	8,374	2,195,048
CO	10	100,590	0	0	4,500	0	100,590	4,500	105,090
CT	7	38,287	1	0	0	0	38,288	0	38,288
DE	6	40,812	0	0	0	230	40,812	230	41,042
FL	119	4,259,337	1	0	4,862	61,840	4,259,700	66,340	4,326,040
GA	59	3,347,294	7	0	956	1,560	3,347,301	2,516	3,349,817
IA	21	712,311	No data	0	4,044	253	712,311	4,297	716,608
ID	3	166,603	No data	0	0	0	166,603	0	166,603
IL	50	1,124,354	11	0	113,965	58	1,205,331	33,057	1,238,388
IN	90	5,470,677	160	0	48,127	48,461	5,470,837	96,588	5,567,424
KS	24	705,880	0	0	467	0	705,880	467	706,347
KY	29	290,945	71	0	18,263	800	291,016	19,063	310,079
LA	44	704,823	129	0	496,584	0	1,187,861	13,675	1,201,536
MA	14	50,678	0	0	15,179	369	50,678	15,548	66,226
MD	10	419,548	0	0	0	0	419,548	0	419,548
ME	7	65,572	No data	0	0	1,747	65,572	1,747	67,319
MI	43	1,656,863	49	0	9,627	2,638	1,656,928	12,249	1,669,177
MN	30	1,128,972	0	0	1	1,410	1,128,972	1,411	1,130,383
MO	31	820,328	0	0	0	1,841	820,328	1,841	822,169
MS	13	536,877	10	0	310,794	0	536,887	310,794	847,681
MT	3	1	No data	0	0	0	1	0	1
NC	66	1,617,112	0	0	13,718	27,822	1,620,882	37,770	1,658,652
ND	4	281,137	5	0	0	0	281,142	0	281,142
NE	9	144,188	0	0	3,103	2	144,438	2,855	147,293
NH	5	49,891	No data	0	0	0	49,891	0	49,891
NJ	23	167,841	69	0	0	0	167,910	0	167,910
NM	2	21,387	No data	0	6	0	21,387	6	21,393
NV	7	47,800	0	0	1,959	0	47,800	1,959	49,759
NY	18	99,248	360	0	83	113	99,608	196	99,804
OH	123	1,583,501	17	0	388,345	4,834	1,583,518	393,179	1,976,697
OK	25	574,291	0	0	110	0	574,291	110	574,401
OR	21	901,084	0	0	3,617	0	901,084	3,617	904,701
PA	60	1,154,378	25	0	89,876	8,555	1,154,403	98,431	1,252,834

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PR	5	43,422	0	0	32,400	99,360	43,422	131,760	175,182
RI	4	61,640	No data	0	0	0	61,640	0	61,640
SC	47	1,499,535	0	115	531,750	306	1,499,535	532,171	2,031,706
SD	3	47,512	No data	0	0	0	47,512	0	47,512
TN	47	4,495,679	255	0	89,127	119	4,495,934	89,246	4,585,179
TX	166	4,271,673	754	425,575	97,903	237,905	4,698,326	335,484	5,033,810
UT	8	45,615	No data	0	8	2	45,615	10	45,625
VA	22	483,346	No data	0	776	0	483,346	776	484,122
VT	1	12,441	No data	0	0	0	12,441	0	12,441
WA	25	1,275,024	40	0	0	2,285	1,275,064	2,285	1,277,349
WI	48	1,480,404	No data	0	30,095	16,686	1,480,404	46,781	1,527,186
WV	14	393,651	5	0	20,828	1,000	393,736	21,748	415,484
WY	1	14,559	No data	0	0	0	14,559	0	14,559
Total	1,558	47,297,934	4,043	425,690	2,439,081	523,967	48,297,213	2,393,502	50,690,715

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

RF = reporting facilities; UI = underground injection

Source: TRI06 2008 (Data are from 2006)

distance for gasoline-powered vehicles and 1.4–2.1 mg/km for diesel trucks have been reported (Hampton et al. 1983). Styrene may also be emitted into the air by other combustion processes. Styrene has been identified in the stack emissions from waste incineration (Junk and Ford 1980), and Kleindienst et al. (1986) reported the presence of styrene in wood smoke emissions, but no quantitative data were reported.

Emissions of styrene from building materials (carpets, floor tiles, insulation), office copiers, and consumer products (disinfectants, plastics, paint, cigarettes) may contribute significantly to indoor air pollution (Crump 1995). A styrene emission rate from glued carpet of 98 ng/minute/m^2 was calculated by Wallace et al. (1987b), and Girman et al. (1986) identified styrene as a major emittant from adhesives used in the constructing and finishing of buildings. Hodgson et al. (1993) determined an average styrene emission rate from new carpets of 410 ng/minute/m^2 over a 24-hour time period, but this was reduced to 30 ng/minute/m^2 when emissions were measured over 168 hours. Carpet cushioning material showed higher styrene emission rates of 2,300 ng/minute/m^2 when measured over 6 hours, but this material also showed significantly lower emission rates of 83 ng/minute/m^2 when measured over a longer span of 96 hours (Schaeffer et al. 1996). Polystyrene products such as packaging materials, toys, housewares, and appliances that may contain small amounts of the monomer also contribute to air levels. The workplace or home office may have substantial levels of airborne styrene due to emissions from laser printers and photocopiers. In the case of laser printers, styrene concentrations measured in test chambers during printer operation were reported to be as high as 380 μg/m^3 (87 ppmv) (Kagi et al. 2007). For photocopiers, emission rates from four different copiers averaged 3,300 μg/hour, but one copier had an emission rate of 12,000 μg/hour (Leovic et al. 1996). General workplace styrene concentrations ranged from 89 to $1.5x10^6$ μg/m^3 (20–$3.4x10^5$ ppmv). Styrene has also been detected in sidestream smoke emitted from cigarettes but concentrations were not reported (IARC 1979).

6.2.2 Water

Estimated releases of 4,043 pounds (~1.83 metric tons) of styrene to surface water from 1,558 domestic manufacturing and processing facilities in 2006, accounted for about 0.01% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). These releases are summarized in Table 6-1.

The principal sources of styrene releases to water are industrial effluents. Styrene has been detected in effluents from chemical, textile, latex, and coal gasification plants (EPA 1976; Pellizzari et al. 1979). Styrene was also identified in one of 63 industrial effluents at a concentration of <10 μg/L (EPA 1979b).

Styrene occurred at concentrations up to 83 µg/L in coal gasification effluents (Pellizzari et al. 1979), and King and Sherbin (1986) reported styrene concentrations up to 970 µg/L in chemical plant effluents. The daily styrene loading from a single chemical plant into the St. Clair River (just south of Lake Huron on the Michigan/Ontario border) was estimated at 133 kg (King and Sherbin 1986). Styrene was detected (but not quantified) in the leachate from an industrial landfill in a study of 58 municipal and industrial landfill leachates (Brown and Donnelly 1988). Styrene has also been detected at trace concentrations in the River Elbe at two different sampling locations, with concentrations ranging from 6.1 to 46 ng/L (Gotz et al. 1998).

6.2.3 Soil

Estimated releases of 2.44 million pounds (~1,110 metric tons) of styrene to soils from 1,558 domestic manufacturing and processing facilities in 2006, accounted for about 5% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 0.426 million pounds (~193 metric tons), constituting about 0.8% of the total environmental emissions, were released via underground injection (TRI06 2008). These releases are summarized in Table 6-1.

Soil and sediments may become contaminated with styrene by chemical spills, landfill disposal of styrene-containing wastes, or discharge of styrene-contaminated water. A small amount of styrene is produced naturally through the activities of microorganisms, and some plants also produce styrene that may be released to soil. The amounts released to soil through these processes, however, are not expected to be significant in comparison to human activities that generate and release styrene to soil.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Should styrene be released to the environment, its vapor pressure indicates that it will partition to the atmosphere. In the atmosphere, styrene exists as a vapor. Styrene is an oily liquid that is slightly volatile; its vapor pressure has been determined to be approximately 5 mm Hg at 20 °C (Verschueren 2001). A small fraction of the styrene released to the atmosphere may dissolve into condensed water vapor such as clouds and raindrops. A Henry's law constant (H) is a measure of the tendency of a chemical to partition between its gas phase and water. A value for H has not been experimentally measured for styrene, but it may be estimated by dividing the vapor pressure of styrene by its solubility in water at the same temperature (EPA 1982a). In this case, the value of H is approximately 2.61×10^{-3} atm-m^3/mole at 25 °C.

Analogous air-water partition coefficients were measured at 37 °C, yielding a value of approximately $5.4x10^{-1}$ atm-m^3/mole (Sato and Nakajima 1979). The magnitude of these values suggests that only a small fraction of vapor-phase styrene would dissolve into atmospheric water droplets. Physical processes such as precipitation and dry deposition would not be significant mechanisms for removing styrene from the atmosphere because of its high photochemical reactivity (EPA 1984b).

Should styrene be released to lakes, rivers, streams, or other waterways, the magnitude of the estimated Henry's law constant ($2.61x10^{-3}$ atm-m^3/mole, assuming a water solubility of 300 mg/L at 20 °C [Verschueren 2001]) and its water solubility suggest that a large fraction of the chemical dissolved in the water will volatilize into the atmosphere (depending on temperature gradients, relative humidity, air currents, and the extent of mixing of the solution). From a modeling perspective, it should be pointed out that the dependence of this process depends on an accurate determination of the chemical's water solubility. In this case, while styrene is only sparingly soluble in water, the reported values are not precise, and range from 160 mg/L at 23 °C to 310 mg/L at 20 °C to 400 mg/L at 40 °C (Banerjee et al. 1980; Valvani et al. 1981; Verschueren 2001). Therefore, estimated rates of volatilization have some uncertainty associated with them. Volatilization of styrene, however, has been measured in surface lake and distilled water samples such that different loadings of styrene were examined. When 2–10 mg of styrene was added to 1 L of lake water, 50% was lost to the atmosphere in 1–3 hours. For the distilled water, volatilization occurred more slowly, with 50% loss occurring within 6–7 hours (Fu and Alexander 1992). The volatilization half-life of styrene in moving water that is 1 meter deep (assuming a solubility of 300 mg/L) may be on the order of 6 hours, based on the empirical relationship reported by Dilling (1977) for the volatilization of chlorinated hydrocarbons from water. The half-life of styrene in the Rhine River was estimated from field measurements at about 14 hours, but it was not known if the loss was due to volatilization, biodegradation, or photodegradation (Zoeteman et al. 1980). Volatilization from ponds and lakes is estimated to be slower, with half-life estimates ranging from 3 to 13 days (EPA 1984b).

Styrene released to soils or sediments will also likely volatilize to the atmosphere, but the rate of this process depends on the characteristics of the soil or sediment. The extent of adsorption of sparingly water-soluble compounds such as styrene is often correlated with the organic carbon content of the adsorbent (i.e., the soil or sediment; Hassett et al. 1983). When adsorption is expressed as a function of organic-carbon content, an organic carbon/water partition coefficient (K_{oc}) is generated, and may be used to rank the relative mobility of the chemical in soil. A K_{oc} value for styrene has not been experimentally measured, but may be estimated from its solubility in water, using the empirical regression of Hassett et al. (1983). Assuming that the solubility of styrene is 300 mg/L, a calculated K_{oc} value for styrene is 260.

The magnitude of this estimated K_{oc} suggests that styrene is "moderately mobile" in soil (Roy and Griffin 1985). In surface soils, where the amount of organic carbon will be highest, the movement of styrene will therefore be retarded by adsorption. In deeper subsurface environments where the amount of organic carbon may be lower, adsorption may not be as significant. The transport of styrene in aquifers by the movement of groundwater contaminant plumes has been observed (Colombani et al. 2009; Roberts et al. 1980). Based on field measurements, the rate of movement of styrene in an aquifer was about 80 times slower than that of the groundwater (Roberts et al. 1980). The slower rate of movement was attributed to adsorption. No information was located to corroborate the estimated K_{oc} value, and apparently, there are no studies in which the adsorption-desorption characteristics of styrene by soils and sediments have been measured.

The octanol/water partition coefficient (K_{ow}) reflects the partitioning of a chemical between octanol and water and is believed to be a good indication of the tendency for a chemical to accumulate in the fatty structures in plants and animal tissues (Kenaga and Goring 1980). The K_{ow} of styrene has been measured to be 1,445 (Banerjee et al. 1980), 891 (log K_{ow}=2.95) (Hansch et al. 1995), and 891 (Valvani et al. 1981), suggesting that styrene will partition to fat tissues. This is shown to be the case by the work of Engstrom et al. (1978a) and EPA (1986d).

Even though styrene does tend to partition into fat, it does not tend to bioaccumulate to high levels, mainly because of its metabolism and excretion. A bioconcentration factor (BCF) relates the concentration of a chemical in an organism to the concentration of the chemical in the medium in which it is exposed. Based on the empirical regression of Kenaga (1980), the BCF for styrene is about 25. An experimentally-measured BCF for goldfish was 13.5 (Ogata et al. 1984). These low BCFs suggest that bioconcentration is not a significant fate of styrene released into the environment (EPA 1984b). No other measured BCFs were located to corroborate these reported values.

6.3.2 Transformation and Degradation

6.3.2.1 Air

The major fate of atmospheric styrene is determined by the rate of photooxidation. Styrene may be transformed by direct photolysis, but the half-life of this process may be on the order of 50 years (EPA 1984b). Kopczynski et al. (1972) found that styrene was not degraded by direct photolysis after 6 hours of exposure.

Styrene is more quickly photooxidized by ozone and hydroxyl radicals. The rate constant for the reaction of styrene with ozone at ambient temperatures (about 25 °C) has been measured and is approximately 0.17–2.16x10^{-19} cm^3/molecule-second (Atkinson et al. 1982; EPA 1979a). Assuming that the mean concentration of ozone in the troposphere is 10x10^{12} molecules/cm^3 (EPA 1980), the half-life of styrene would be approximately 13 hours. The rate constant for the reaction of styrene with hydroxyl radicals has been measured as 5.3x10^{-11} cm^3/molecule-second (Bignozzi et al. 1981). Assuming that the concentration of tropospheric hydroxyl radicals varies from 3x10^5 to 1x10^7 molecules/cm^3 (Mac Leod et al. 1984), it follows that the atmospheric half-life of styrene would be between 0.5 and 17 hours. More recent studies provide a similar rate constant of 5.9x10^{-11} cm^3/molecule-second (Bunce and Dryfhout 1992) and 5.8x10^{-12} cm^3/molecule-second (EPA 1993a), with a corresponding half-life of ~2.2 hours. Consequently, it is not expected that styrene will persist in the atmosphere, due to the combined and rapid effects of ozone- and hydroxyl radical-initiated atmospheric degradation processes. Transformation products resulting from such degradation processes include primarily oxygen-containing hydrocarbons such as phenol, phenylacetaldehyde, and phenoxy radical (Sloane and Brudzynski 1979) or other compounds (Atkinson and Arey 2003), as well as other aromatic hydrocarbons such as the benzyl radical and other unsaturated hydrocarbons (Sloane and Brudzynski 1979).

6.3.2.2 Water

Little is known about abiotic transformations of styrene in water. The reaction of styrene with peroxy radicals appears to be too slow to be significant (EPA 1984b), and no relevant information regarding photochemical reactions in water was located. There is no information that styrene will hydrolyze in water, nor would its chemical structure suggest such potential.

While little is known about the abiotic degradation potential of styrene in water, it has been shown to be biologically degraded in several types of aquatic systems including sewage treatment facilities, biofilm reactors, groundwater, and lakes. In sewage samples, styrene showed a range of biodegradability. In one study where styrene was added at a concentration of 1 mg/L, 20% of the added styrene was completely degraded (i.e., mineralized to CO_2) within 3 days, with >60% degraded within 30 days (Fu and Alexander 1992). In another sewage fate study, however, styrene was only slightly biodegraded; in five different evaluations, conducted for either 17 or 36 days, styrene degradation ranged from 6 to 23% (Pahren and Bloodgood 1961). Bridie et al. (1979) found that 42% of the styrene initially present degraded in 5 days when unadapted sewage was used as the source of microorganisms; when an adapted sewage was used,

80% degradation was observed. Very low concentrations of styrene (<10 µg/L) were completely degraded within 20 minutes in an aerobic biofilm reactor after acclimation, but the chemical was degraded much more slowly (~8% after 2 days) under methanogenic biofilm column conditions (Bouwer and McCarty 1984). When studied in groundwater, styrene biodegradation ranged between 4 and 12% per week (when added at 600–800 µg/L; Wilson et al. 1983) and a more recent study showed similar rates of degradation, with over 40% mineralization after 30 days (Fu and Alexander 1992). Styrene had a similar degradation potential in lake water, with ~35% degradation after 30 days (Fu and Alexander 1992).

6.3.2.3 Sediment and Soil

Styrene is rapidly degraded in most soils when incubated under aerobic conditions, but it persists when soil conditions are anaerobic (e.g., waterlogged). Styrene was rapidly degraded when added to either a low organic-matter content landfill soil or a high organic-matter content loamy soil. When added at 2 g/kg, >87% of the styrene was degraded in the landfill soil, and >95% was degraded in the loamy soil (measured over a period of 16 weeks; Sielicki et al. 1978). When styrene was added to the soils at higher concentrations (5 g/kg), degradation was slower and less was degraded, with ~60% degraded in both soils after a 16-week incubation. Fu and Alexander (1992) showed that styrene was biodegraded in loamy soil (when added at 2 mg/kg soil), with >50% degradation occurring over a 30-day incubation period, and the same soil in a later study showed similar amounts of degradation (40% degradation in 50 days; Fu et al. 1994). In contrast to the findings in aerobic soils, this research group showed that styrene persisted when soil conditions were waterlogged and anaerobic (Fu and Alexander 1996). Other researchers, however, have been able to demonstrate degradation of styrene under anaerobic conditions by consortia of microbial cultures (Grbic-Galic et al. 1990). The relevance of these consortia studies to actual environmental samples is unknown.

Several bacterial and fungal species have been isolated from soils that are capable of using styrene as a sole-carbon source (Braun-Lüllemann et al. 1997; Burback and Perry 1993; Hartmans 1995; Sielicki et al. 1978; Warhurst and Fewson 1994), and these organisms degrade styrene by either side chain oxidation or aromatic ring attack. Initial biodegradation products included styrene oxide, 1-phenylethanol, 2-phenylethanol, and then phenylacetaldehyde, acetophenone, and phenylethanediol, and then phenylacetic acid, with degradation proceeding towards normal metabolic intermediates such as acetaldehyde and pyruvate (Warhurst and Fewson 1994).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to styrene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of styrene 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 styrene 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 styrene in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Styrene is a common contaminant of ambient urban air. Concentrations of styrene greater than rural air concentrations have been identified in urban and industrial source areas, near hazardous waste sites, in motor vehicle tunnels, in indoor air, and in workplace environments. A summary of monitoring data for these locations is presented in Table 6-2. The data suggest that indoor air concentrations of styrene can be considerably higher than outdoor concentrations. Cigarette smoke has also been implicated as a significant source of styrene in indoor air (EPA 1987e; Vainiotalo et al. 2008; Wallace et al. 1986a), as has the operation of photocopying machinery (Stefaniak et al. 2000; Leovic et al. 1996, 1998) and laser printers (Kagi et al. 2007).

Monitoring studies in Minnesota detected styrene in over 1,400 air samples collected from a total of 2,507 samples (there were 1,004 samples where styrene was below the detection limits) over an 8-year period. The average concentration detected was 0.1 μg/m^3 (0.02 ppmv); the median concentration detected was 0.08 μg/m^3 (0.02 ppmv); and the maximum detected amount was 1.49 μg/m^3 (0.343 ppmv) (Pratt et al. 2000). Styrene monitoring in ambient air conducted in Chiba City, Japan over an 8-week period showed slightly higher mean concentrations, ranging from 0.11 to 0.36 μg/m^3 (0.025–0.083 ppmv) (Uchiyama and Hasegawa 2000).

6.4.2 Water

Styrene is not frequently found in U.S. water supplies. Styrene was not detected in any of the >1,000 samples of drinking water analyzed during three federal surveys (EPA 1985a), but had been reported occasionally in drinking water supplies in several states (Coleman et al. 1984; EPA 1975, 1976; Kleopfer and Fairless 1972; Kool et al. 1982; Sanjivamurthy 1978) well water (EPA 1985b; Krill and

Table 6-2. Styrene Concentrations in Representative Air Samples

Location	Concentration (μg/m^3) Maximum	Mean	References
Indoor			
Indoors, unspecified	6,500	0.4–8.9 0.3–50	EPA 1987e, 1988c; Fishbein 1992; Sakaguchi and Akabayashi 2003; Shields and Weschler 1992; Wallace et al. 1986a
New homes	14.3	0.9–2.6	Hodgson et al. 2000
Remodeled buildings	167	0.1–10.1	Rothweiler et al. 1992; Zabiegala 1999
Workplaces	4.5x10^6	<1–1.5x10^6	Bartolucci et al. 1986; Cocheo et al. 1983; Correa et al. 2004; Fishbein 1992; Kagi et al. 2007; NIOSH 1983
Photocopy centers	12,000[a]; 220[b]	7,000[a]; 89[b]	Stefaniak et al. 2000; Leovic et al. 1996, 1998
Restaurants	3.3	1.6	Vainiotalo et al. 2008
Outdoor			
Rural/suburban	53	0.28–0.34[c]; 0.43	EPA 1988c; Graedel 1978; Islam and Stancheva 1999; Kinney et al. 2002
Urban	2,500	0.29–3.8; 20	EPA 1987e, 1988c; Fishbein 1992; Grosjean and Fung 1984; Grosjean et al. 1998; Harkov et al. 1985; Wallace et al. 1986b
Industrial source areas	25	1.3[c]–2.1	EPA 1978, 1983, 1988c
Municipal waste sites	6,100	No data	Assmuth and Kalevi 1992; Eitzer 1995
Hazardous waste sites	65	1.1–6.4	Harkov et al. 1985; La Regina and Bozzelli 1986
Tunnels	46	1.1–6.6[d]	Hampton et al. 1983; Zielinska et al. 1996

[a]Value provided is the emission rate, as μg/hour; the emission rate was measured during operation of copier in test chambers.
[b]Value provided is the emission rate, as μg/hour; the emission rate was measured during the idle phase of copier operation in test chambers.
[c]Median value
[d]Range of values, no mean given.

Sonzogni 1986), river water (EPA 1976; Sheldon and Hites 1978), and Lake Erie (Konasewich et al. 1978). Quantitative data were not available in these reports. A more recent survey provided by the EPA National Contaminant Occurrence Database (EPA 2006) noted that styrene was detected rarely in groundwater, where it was detected only 295 times out of over 174,000 analyses (<0.2% of the samples); detected concentrations ranged from <10 to 40 μg/L. Styrene concentrations in raw and treated waters ranged from 0.1 to ≥1.0 μg/L in an evaluation of organic compounds in Canadian water supplies at nine municipalities along the Great Lakes (Otson 1987). Styrene was rarely detected in aquifer materials in a large evaluation of U.S. groundwater and wells conducted by the U.S. Geological Survey (USGS). For >3,400 test evaluations of aquifer materials, there was a very low frequency of detections, with the median concentration being 0.015 μg/L. It was detected less frequently and also at low concentrations in domestic wells (0.014 μg/L), and at slightly higher concentrations in public wells (median=0.13 μg/L) (USGS 2006).

Other bodies of water—those potentially highly contaminated and those that are used for direct ingestion—likewise do not usually contain styrene. Styrene is not commonly detected in groundwater even near superfund sites, and was not found in a drinking water evaluation of public water sources in Torino, Italy (Canter and Sabatini 1994; Zelano et al. 1998). In a study of wells near a superfund site in Florida, styrene was detected at a very low concentration (the maximum detected concentration was 6.3 μg/L) near the site, but it was not detected in any treated water effluents (Canter and Sabatini 1994). Squillace et al. (1999) surveyed a vast number of drinking water wells in the United States over a 10-year period. Styrene was detected in <1% of the 2,900 surveyed urban and suburban wells between 1985 and 1995, and the concentrations detected were >2 orders of magnitude lower than the health advisory level. Styrene was only detected in rural wells, not in urban ones. Finally, Zelano et al. (1998) did not report the detection of any styrene in an evaluation of 21 public drinking water fountains in Torino, Italy.

6.4.3 Sediment and Soil

Limited data were located regarding estimation of styrene in sediments and soils (see Section 6.2.3). Water and sediment samples from the Lower Tennessee River were evaluated for styrene, and low concentrations (4.2 ppb) were found (Goodley and Gordon 1976).

6.4.4 Other Environmental Media

Styrene is a natural component of many foods; however, most styrene associated with food is the result of packaging of the food material in polystyrene containers. Styrene has been found as a natural component of roasted filberts, dried legumes, fried chicken, cooked pork, roasted beef, mussels, clams, eggs, nectarines, and Beaufort cheese (Dumont and Adda 1978; Kinlin et al. 1972; Lovegren et al. 1979; Takeoko et al. 1988; Tang et al. 1983, 2000), but detected concentrations were often very low (Tang et al. 2000), except for turkey sausage, where detected levels were 100 ppb, and in some cheeses, where concentrations detected were up to 5,000 ppb (Tang et al. 2000). In contrast, styrene is a natural component of cinnamon, with concentrations up to 40,000 ppb (Tang et al. 2000). Data on styrene levels from an FDA monitoring study (1996–2000) of volatile organic compounds in food items are presented in Table 6-3 (Fleming-Jones and Smith 2003).

Styrene may enter packaged foods by migration from polystyrene food containers and packaging materials, with concentrations ranging from <100 to >3,000 ppm, but common levels being much lower (5–30 ppb) (EPA 1985a; Tang et al. 2000). Concentrations of styrene measured in yogurt packaged in polystyrene containers ranged from 5.5 to 150 ppb (Withey 1976). Mean levels of styrene in foods packaged in plastic in the United Kingdom ranged from <1 to 180 ppb (Gilbert and Startin 1983). Similar concentrations of styrene were detected in other dairy products packaged in polystyrene containers (IARC 1979). The rate of styrene migration into food is mainly a function of the diffusion coefficient of the monomer in the polymer and of the lipophilicity of the food (Till et al. 1987). For example, 4–6% of the free monomer in polystyrene packaging migrated into corn oil or sunflower oil within 10 days, while only 0.3–0.6% migrated into milk, beef, or water. Similarly, migration of styrene from foam cups into liquids such as water, tea, or coffee was about 8 ng/cm^2, while migration into 8% ethanol (as might be encountered in wine or other alcoholic drinks) was 36 ng/cm^2 (Varner and Breder 1981). However, Withey and Collins (1978) found no clear relationship between the styrene monomer content of packaging material (which varied widely) and the amount leached into food after comparable residence times. Levels of styrene ranged from 0.50 to 46.40 ppb in bottled water stored in 200–250 mL polystyrene containers (Al-Mudhaf et al. 2009). Concentrations in the water increased with time, indicating that the source was migration from the container walls. These authors did not detect styrene in bottled water stored in polyethylene terephthalate (PET) containers.

Styrene has been identified as a component of cigarette smoke (EPA 1984b; Vainiotalo et al. 2008) and has been detected in concentrations of 18 μg/cigarette in the smoke of cigarettes made in the United

Table 6-3. Styrene Levels in Food Items

Food	Number of detections	Minimum (ppb)	Maximum (ppb)
American cheese	4	2	11
Cheddar cheese	3	4	70
Mixed cuts	14	21	104
Ground beef	6	4	13
Pork bacon	7	6	85
Cream cheese	2	2	3
Frankfurters, beef	8	4	77
Chocolate cake with icing	12	7	57
Tuna canned in oil	1	2	2
Fruit flavored cereal	3	2	10
Eggs, scrambled	6	5	10
Peanut butter	13	16	38
Avocado, raw	8	3	550
Popcorn, popped in oil	3	2	2
Blueberry muffin	10	8	141
Strawberries, raw	9	12	350
Orange, raw	2	2	3
Coleslaw with dressing	1	2	2
Sweet roll/Danish	13	13	91
Potato chops	6	2	16
Popsicle	3	4	11
Quarter pound hamburger, cooked	6	4	27
Margarine	10	9	20
Sandwich cookies	14	15	165
Butter	12	11	28
Chocolate chip cookies	12	15	111
Sour cream	3	5	30
Apple pie, fresh/frozen	9	10	40
Chicken nuggets	12	10	66
Graham crackers	6	4	21
French fries	12	8	68
Cheeseburger, quarter pound	5	5	22
Cheese pizza	6	3	23
Bologna	7	2	78
Cheese and pepperoni pizza	7	8	20
Olive/safflower oil	11	3	54
Sugar cookies	14	24	142
Cake doughnuts with icing	10	6	45

Source: Fleming-Jones and Smith (2003).

States (IARC 1979). Indoor air concentrations of styrene may be significantly higher in homes of smokers than nonsmokers (EPA 1987e).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to styrene may occur by inhalation, ingestion, or dermal absorption. The most likely mode of exposure of the general population to styrene is by inhalation of indoor air (EPA 1985a). Based on the EPA (1989e) estimate that the average person spends 20.4 hours/day indoors (inhaling about 17 m^3 of air during that time based on an air inhalation rate of 20 m^3/day) and the range of mean indoor air concentrations presented in Table 6-2, typical indoor exposure levels to styrene may range from 1.7 to 850 μg/day. Additional exposures may occur from inhalation of outdoor air and ingestion of food that was stored in polystyrene containers. Vitrac and Leblanc (2007) estimated a median styrene intake ranging from 1 to 35 μg/day per person for household exposures resulting from migration of this substance from food packaging. Based on estimated food consumption rates, Tang et al. (2000) reported an estimated annual general population exposure to styrene ranging from 0.8 to 4.5 mg/person from food. Outdoor air concentrations are likely to be lower in rural than urban areas and are likely to be small compared to indoor air concentrations. Exposure from municipal drinking water is probably insignificant. However, groundwater at hazardous waste sites where styrene has been detected may provide significant exposure to styrene if used as a local water supply.

The exposure of the population to styrene varies significantly from the typical to the worst-case scenario. The daily general population exposure to styrene via food has been estimated at 0.2–1.2 μg/person and the exposure via inhalation has been estimated at 18–54 μg/person, with a total estimated exposure ranging from 18.2 to 55.2 μg/day. This is equivalent to 6.7–20.2 mg/year. Therefore, the primary route of exposure for the general population is via inhalation (Tang et al. 2000). Worst-case exposure estimates, on the other hand, are 0–0.5 μg/day from drinking water, 30 μg/day from food, and 65,000 μg/day from air (EPA 1985a). These estimates are based on the highest levels estimated or monitored and, therefore, reflect the highest potential exposure rather than typical exposure for the general population.

Exposure of the general population to styrene is confirmed by human monitoring data. Styrene has been identified in adipose tissue at concentrations of 8–350 ng/g (EPA 1986d), in blood at a mean concentration of 0.4 μg/L (Antoine et al. 1986), and in exhaled breath at mean concentrations of 0.7–1.6 μg/m^3 (EPA 1987e).

A large number of workers are potentially exposed to styrene. NIOSH estimates that approximately 300,000 workers at 22,000 facilities may be exposed to styrene (NIOSH 1990); about 30,000 of these on a full-time basis (NIOSH 1983) and about 86,000 are females. The highest potential exposure occurs in the reinforced-plastics industry, where workers may be exposed to high air concentrations and also have dermal exposure to liquid styrene or resins (Dalton et al. 2007; Fustinoni et al. 2008; Lemasters et al. 1985; NIOSH 1983; Rihs et al. 2008; Sato et al. 2009; Triebig et al. 2008; Van Rooij et al. 2008). Hemminki and Vianio (1984) estimated that heavily exposed workers in this industry in Finland might be exposed to up to 3 g of styrene per day. Van Rooij et al. (2008) estimated that styrene levels ranged from 30 to 222 mg/m^3 in the breathing zone of European open-mold process workers in 2003. Table 6-4 lists levels of styrene measured in the blood, urine, and surrounding air of reinforced plastic workers. Urinary levels of styrene metabolites are also included. Significant occupational exposures may also occur in other industrial settings, including styrene polymerization, rubber manufacturing, and styrene-polyester resin facilities (Engstrom et al. 1978b; NIOSH 1983; Rappaport and Fraser 1977) as well as in photocopy centers or facilities (Leovic et al. 1996, 1998; Stefaniak et al. 2000). Fustinoni et al. (2008) found that concentrations of styrene and its metabolites measured in the urine of 13 varnish workers were comparable to those measured in fiberglass reinforced plastic workers.

6.6 EXPOSURES OF CHILDREN

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

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

Children can be exposed to styrene at home by inhalation of contaminated air and by food consumption. Inhalation-based exposures may occur in both urban and rural home environments, both of which may be contaminated by vehicular and industrial emissions. In addition, exposure to tobacco smoke may provide

Table 6-4. Concentrations of Styrene in the Surrounding Air, Blood, and Urine of Reinforced Plastics Workers, Including Urinary Concentrations of the Styrene Metabolites, MA and PGA

	Styrene			MA	PGA	
Occupation	Air (ppm)	Blood (µg/L)	Urine (µg/L)	Urine (mg/g creatinine)	Urine (mg/g creatinine)	Reference
Boat building (n=248)						Triebig et al. 2008
Mean	<10–40[a]	53.9–108	–	40.7–742	10.6–228	
Boat building (n=67)						Sato et al. 2009
Mean	51.7	–	47.0	300	120	
Minimum	0.3	–	5.2	0.00	0.00	
Maximum	133.5	–	189.2	1.81	0.48	
Boat building (n=88)						Rihs et al. 2008
Mean	55.1–82.0	203.1–264.2	–	–	83.8–190.0	
Minimum	0.2	55.8	–	–	24.3	
Maximum	690.7	662.0	–	–	591.3	
Unspecified reinforced plastics (n=8)						Fustinoni et al. 2008
Mean	4.20	–	1.9–7.5	32.29–148.13	50.05–77.97	
Minimum	0.53	–	1.1	13.04	17.26	
Maximum	21.57	–	29.7	515.12	248.99	
Boat building (n=30)						Dalton et al. 2007
Mean	0.6–22[a]	–	–	–[b]	–[b]	

[a]Levels were calculated based on urinary levels of MA+PGA.
[b]Mean concentrations ranging from 10 to 463 mg/g creatinine were reported for the sum of MA+PGA in urine.

– = not reported; MA = mandelic acid; PGA = phenylglyoxylic acid

another route of styrene exposure, especially in homes where one or both parents, any siblings, or other relatives smoke. Children may be also be exposed to higher levels of styrene indoors at home during painting of indoor rooms, especially during winter months (such as over winter school vacations) when the child stays indoors more and during which time, windows may not be opened.

From a food-based exposure perspective, infants may be exposed to styrene from consuming food items such as those listed in Table 6-3. In addition, it is possible that exposure may also result from consumption of infant formula or from nursing practices. In the 5-year FDA study on volatile organic compounds in foods (Fleming-Jones and Smith 2003), soy- and milk-based infant formula was included in the study; however, the results for styrene were not reported. Baby foods and infant formula are often stored in polystyrene containers and the migration of low levels of non polymerized styrene into food items from polystyrene containers has been demonstrated (EPA 1985a; Tang et al. 2000). In a study on chemicals in mother's milk, styrene was identified, but not quantified, in 8 out of 12 samples of mother's milk samples collected from mothers living in four U.S. urban areas (Pellizzari et al. 1982). Duffy and Gibney (2007) estimated the styrene exposure of Irish children between the ages of 5 and 12 years as a result of the migration of styrene from food packaging. The calculated mean styrene intake was 0.122 µg/kg body weight-day when using 90th percentile migration values and 0.169 µg/kg when using maximum migration values. The authors note that these values are well below the provisional maximum tolerable daily intake of 40 µg/kg body weight-day established by the Joint FAO/WHO Expert Committee on Food Additives. Although children are exposed to styrene from the oral routes mentioned above, it has been estimated that >90% of human exposure to styrene arises due to inhalation routes (Fleming-Jones and Smith 2003; Tang et al. 2000).

Aside from food-related intake, children's exposure to styrene may differ from exposures to adults, especially during school, home, or play activities that may expose the children to styrene sources. For example, for elementary aged children (grades 2, 3, 4, and 5) attending inner city schools in Minneapolis, it was found that the lowest exposure to styrene occurred either outdoors or in school, and the highest exposure occurred at home. The latter can be substantially influenced (increased) if smoking occurs in the home. Exposures to styrene while outside, in either winter or spring, were very low (winter: 0.0 µg/m^3; spring: 0.1 µg/m^3), whereas exposures were much higher at school (winter: 31.3 µg/m^3; spring: 39.7 µg/m^3), but were almost three times higher at home (winter: 91.9 µg/m^3; spring: 91.9 µg/m^3) (Adgate et al. 2004). These exposures led to blood level concentrations of styrene that were generally twice as high as the general population (Sexton et al. 2005).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

People working in various styrene industries are likely to have the highest exposures to styrene. Lower levels may be encountered near industrial facilities or hazardous waste sites emitting styrene to outdoor air. High indoor styrene concentrations in the home may be due to emissions from building materials, consumer products, tobacco smoke, photocopiers and laser printers. Smokers and those eating a high proportion of foods packaged in polystyrene may also have above average exposure to styrene, with the amounts estimated by smoking (100 µg from 20 cigarettes) more than doubling the normal estimated exposure to styrene (Tang et al. 2000). In addition, workers with long-term employment at photocopy centers may also be exposed to high concentrations of styrene.

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

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 solubility of an organic compound in water is indicative of how that chemical will partition between water, soil, and organisms (Banerjee et al. 1980; Hassett et al. 1983; Valvani et al. 1981). Clarification of the exact solubility of styrene in water would be helpful because a range of values is currently reported (Table 4-2). The Henry's law constant and K_{oc} value for styrene need to be verified experimentally to provide more accurate predictions of air-water and soil-water partitioning.

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 2005, became available in May of 2007. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Substantial quantities of styrene are currently produced and used in the United States (Heylin 1989; HSDB 2009; SRI 1989; USITC 1988). Production and import quantities, producers, and uses are well documented, with $4.7x10^{12}$ g produced in 2000 (HSDB 2009), representing a slight increase in U.S. production since 1997 ($3.12x10^{12}$ g). The United States has imported less styrene over the last several decades, with amounts decreasing more than an order of magnitude, from $1.4x10^{10}$ g imported in 1978 to $5.7x10^{8}$ g being imported in 2001 (HSDB 2009). Interestingly, styrene exports increased from $3.6x10^{10}$ g in 1978 (representing 1% of total U.S. production) to $>1.2x10^{12}$ g exported in 2001 (representing >26% of total U.S. production) (HSDB 2009).

Quantities of styrene disposed of by various disposal methods, other than those reported to the TRI, are not known. Styrene releases into water are regulated by EPA, but styrene is not listed as a hazardous waste constituent and, therefore, land disposal restrictions do not apply to this compound. Additional information on disposal methods used for styrene and styrene-containing products and the quantities disposed of by each method would help to better characterize the potential for human exposure to this compound from disposal at waste sites or other locations.

Environmental Fate. Styrene will partition among the environmental media, with a tendency to volatilize from water to air and to adsorb to soils (EPA 1984b; Roberts et al. 1980; Sato and Nakajima 1979). However, data on styrene volatilization from water and confirmation of the estimated K_{oc} value by adsorption/desorption data would be useful to estimate more accurately the tendency of styrene to partition to air and soil. Confirmation of the K_{oc} would also provide a more reliable basis for estimating the mobility of styrene in the various types of soil.

Although the reaction mechanisms of styrene transformations in the atmosphere are fairly well understood (Atkinson et al. 1982; Bignozzi et al. 1981; EPA 1979a; Sloane and Brudzynski 1979), more information regarding the environmental fates of the transformation products would allow a more accurate prediction of the atmospheric fate of this compound. Biodegradation data are available for styrene under both aerobic and anaerobic conditions (Bridie et al. 1979; Grbic-Galic et al. 1990).

Bioavailability from Environmental Media. Styrene is known to be absorbed following inhalation, oral, and dermal contact (Dutkiewicz and Tyras 1968; Engstrom et al. 1978a, 1978b; Ramsey and Andersen 1984; Ramsey and Young 1978; Withey 1976; Withey and Collins 1979). Absorption rates via inhalation are known (Withey and Collins 1978). Additional data are needed to evaluate absorption rates following oral and dermal exposure. It is believed that absorption of styrene from the gut is believed to be generally rapid and therefore, contact with styrene contaminated food, soil, or water will probably also result in significant absorption. However, this may depend on the medium in which it is contained.

Food Chain Bioaccumulation. Bioconcentration of styrene in aquatic organisms is not likely to be significant, based on both a measured BCF for a single goldfish species (BCF=13.5; Ogata et al. 1984) and an estimated BCF (EPA 1984b; Kenaga 1980; Ogata et al. 1984). No data on biomagnification of styrene in the food chain were located. Since significant bioaccumulation is unlikely, this lack of data may not be a major limitation. No data needs are identified at this time.

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

Monitoring data for styrene in environmental compartments are extensive, and historical and recent data are available for air (EPA 1987e, 1988c; Uchiyama and Hasegawa 2000), groundwater (Canter and Sabatini 1994; Squillace et al. 1999), and rivers (Gotz et al. 1998; Rathbun 2000). Additional data on styrene levels in water and soil, especially in the vicinity of hazardous waste sites, would be useful in assessing the potential for human exposure. Estimates of human intake from food, air, water, and soil have been made (EPA 1985a; Tang et al. 2000) and will undoubtedly be revised as additional data become available.

Exposure Levels in Humans. Styrene has been detected in human blood, breath, milk, and adipose tissue of the general population (Antoine et al. 1986; EPA 1986d, 1987e; Pellizzari et al. 1982) and metabolites of styrene have been detected in urine of workers exposed to styrene (Elia et al. 1980; Sollenberg et al. 1988). However, data generated by biological monitoring of populations in the vicinity of waste sites with the most sensitive methods (Section 7.1) would be useful in assessing the magnitude of human exposures from this source.

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

Exposures of Children. Additional studies on the exposure of children to styrene would improve understanding of any mechanisms and pathways for styrene exposure and subsequent effects on this subpopulation. The exposure study report by Adgate et al. (2004) and the corresponding blood level study by Sexton et al. (2005) provide a good understanding for styrene exposures and uptake in one metropolitan area in the Midwestern United States, but additional reports investigating exposures and uptake, for example, in other climates, would be beneficial.

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 styrene 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

No current ongoing studies located in the Federal Research in Progress (FEDRIP) database were related to the potential for human exposure. The Computer Retrieval of Information on Scientific Projects (CRISP 2007) National Institutes of Health database identified one study. Scott Ensign of Utah State University proposed to investigate microbial pathways of short-chain hydrocarbon metabolism and the properties of the enzymes, cofactors, and regulatory elements associated with these pathways. The work will be sponsored by the National Institutes of Health/National Institute of General Medical Sciences and will investigate the central roles of carboxylation and novel cofactors/enzymes in bacterial hydrocarbon/epoxide/ketone metabolism of these chemicals, including styrene, by pursuing the biochemical, structural, and genetic characterization of these processes (CRISP 2007).

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for

Disease Control and Prevention, will be analyzing human blood samples for styrene and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

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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 styrene, its metabolites, and other biomarkers of exposure and effect to styrene. 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.

As a volatile material, styrene is readily determined by gas chromatographic (GC) analysis. As a hydrocarbon, styrene is detected very sensitively by flame ionization detection (FID); its aromatic nature enables some selectivity by photoionization detection (PID); and it can be specifically identified by mass spectrometry (MS). Styrene is usually collected from the gas phase or from vapor evolved from the sample matrix on a column of solid sorbent, such as Tenax®. Cryogenic (low temperature) collection and sorption in organic liquids are also possible.

Capillary gas chromatography, also known broadly as high-resolution gas chromatography (HRGC), has greatly facilitated the analysis of compounds such as styrene that can be measured by gas chromatography and has resulted in vast improvements in resolution and sensitivity. It has made the choice of a stationary phase less important than is the case with the use of packed columns. The instrumental capability to separate volatile analytes by HRGC is, for the most part, no longer the limiting factor in their analysis.

The specific analytical methods used to quantify styrene in biological and environmental media samples are summarized below.

7.1 BIOLOGICAL MATERIALS

Methods have been described for the determination of styrene in expired air (Kneip and Crable 1988a; Stewart et al. 1968; Wallace and Pellizzari 1995; Wallace et al. 1996), blood (Antoine et al. 1986; Ashley et al. 1992; Bartolucci et al. 1986; Chambers et al. 2006; Guillemin and Berode 1988; Withey and Collins 1977), urine (Dolara et al. 1984; Ghittori et al. 1987; Pezzagno et al. 1985), adipose tissue (Engstrom et

al. 1978a), and other tissues (heart, lungs, liver, spleen, kidney, brain) (Withey and Collins 1977) (Table 7-1). These methods generally require styrene release from the sample matrix and collection on a column of solid sorbent or collection as headspace gas; more recent methods permit the exhaled breath to be delivered directly, via a breath interface, to the mass spectrometer (Wallace et al. 1996). Cryogenic collection is also possible (Romieu et al. 1999). Of the available methods for detecting styrene, FID is the most sensitive, and MS is the most specific, the latter of which can be made more sensitive by tandem MS approaches (MS/MS) (Wallace et al. 1996). Levels of detection are in the low parts per billion range for breath samples (Stewart et al. 1968; Wallace et al. 1996) and parts per trillion range for blood samples (Ashley et al. 1992; Chambers et al. 2006).

The major metabolites of styrene in humans are mandelic acid (MA) and phenylglyoxylic acid (PGA). Detection of these metabolites in urine is the most commonly performed procedure as an indicator of exposure to styrene. Procedures have been described for their measurement in urine (Baselt 1988a; Dolara et al. 1984; Engstrom et al. 1976; Kneip and Crable 1988b, 1988c; Korn et al. 1984; Pezzagno et al. 1985; Sedivec et al. 1984; Sollenberg et al. 1988). Generally, these styrene metabolites are converted to volatile derivatives and measured gas chromatographically or determined directly by high performance liquid chromatography (HPLC). Two other styrene metabolites that may result from exposure to styrene are 4-vinylphenol (Pfaffli et al. 1981) and styrene glycol (phenyl ethylene glycol) (Guillemin and Berode 1988), but methods for the detection of these metabolites in biological materials have not been worked out in detail. Sensitive methods are also available for measuring styrene oxide in blood (Kessler et al. 1990; Langvardt and Nolan 1991), although these techniques are probably more useful in research on styrene toxicity than in detecting or quantifying styrene exposure.

Methods for detection of styrene and its metabolites in biological materials are summarized in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

Styrene determined in environmental samples is usually collected on solid sorbents (from air; Zielinska et al. 1996) or on solid sorbents after purging in a gas stream (water, soil, solid waste samples; Miermans et al. 2000)). Styrene from such samples is measured very sensitively by GC/FID and very specifically by GC/MS. Methods for the determination of styrene in environmental samples have been standardized by the American Society for Testing and Materials (ASTM 1988a, 1988b), EPA (1986a, 1986b, 1989c, 1989d, 2003), and NIOSH (1984). Relatively low detection limits can be achieved for the determination of styrene in environmental samples and the accuracy appears to be acceptable for those limited cases in

Table 7-1. Analytical Methods for Determining Styrene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Styrene analyte					
Adipose tissue	Evaporation into nitrogen, collection as vapor	GC	No data	No data	Engstrom et al. 1978a
Breath[a]	Collection in Saran bag	GC/FID	0.05 ppm	No data	Stewart et al. 1968
Breath	Sorption onto silicagel, desorption into headspace	GC	0.1 ppm	No data	Kneip and Crable 1988a
Breath	Collection in Tedlar bag, followed by sorption of VOCs (including styrene) onto Tenax	GC/MS	Low ppb	No data	Wallace et al. 1996
Breath	Collection onto personal monitoring badge, followed by solvent extraction	GC/FID	0.9 ppb[b]	No data	Romieu et al. 1999
Blood	Purge at 40–50 °C with helium, collection on Tenax-GC/silica	GC/MS	No data	CV<5%	Antoine et al. 1986
Blood	Headspace analysis	GC/FID	No data	No data	Bartolucci et al. 1986
Blood	Collection in vacutainer with EDTA as anticoagulant, headspace analysis	GC	No data	No data	Guillemin and Berode 1988
Blood	Headspace analysis	GC	0.02 µg/mL	No data	Withey and Collins 1977
Blood	Vacutainer collection, followed by purge and trap	GC/MS	9 ppt (95% CI: 4–21 ppt)	95–121%	Ashley et al. 1992
Blood	Vacutainer collection, followed by static headspace sampling using solid-phase microextraction	GC/MS	30 ppt (98.15% mean accuracy)	No data	Chambers et al. 2006
Serum	Headspace analysis and solid-phase microextraction	GC/FID	0.013 µg/mL	No data	Barua et al. 2008
Heart, lungs, liver, spleen, kidney, brain	Hemogenate prepared for headspace analysis	GC	0.01 µg/g	No data	Withey and Collins 1977
Urine	Headspace from sample maintained and 37 °C for 2 hours	GC/MS	No data	No data	Ghitori et al. 1987
Urine	Sorption on XAD-2, elution with n-hexane	HPLC/UV	<0.7 µg/L	72±10%	Dolara et al. 1984

Table 7-1. Analytical Methods for Determining Styrene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Headspace analysis	GS/MS	No data	No data	Pezzagno et al. 1985
Styrene metabolite analyte					
Urine for MA	Extraction with ethyl acetate, derivatization to isopropyl ester	GC/FID	No data	No data	Korn et al. 1984
Urine for MA	Extraction with diethyl ether, silylation	GC	No data	No data	Engstron et al. 1976
Urine for MA and PGA metabolites	Extraction and derivatization	GC/FID	0.05 ppm	94% MA, 98% PGA	Bartolucci et al. 1986
Urine for MA metabolite	Acidification, extraction, derivatization	HRGC/FID	10 mg/L	No data	Kneip and Crable 1988b
Urine for PGA metabolite	Reduction, acidification, extraction, derivatization	HRGC/FID	10 mg/L	No data	Kneip and Crable 1988c
Urine for MA and PGA metabolites	Extraction with ethyl acetate, derivatization to methyl esters with diazomethane	GC	10 mg/L	No data	Sedivec et al. 1984
Urine for MA and PGA metabolites	Extraction with ethyl acetate, evaporation derivatization	GC/FID	No data	97–99% relative recovery	Baselt 1988a
Urine for MA and PGA metabolites	Acidification, extraction, evaporation	HPLC/UV	1.1–17.0 ng/mL	99.6–100.9%	Onchoi et al. 2008
Urine for MA, PGA, and hippuric acid metabolites	Direct injection	HPLC/UV	<1 µg/mL[c]	<3% deviation from true value at 5 µg/mL	Regnaud et al. 1987
Urine for MA and PGA (stereo-selective)	Extraction and derivatization	HRGC/FID	No data	No data	Korn et al. 1987
Blood for styrene oxide	Extraction with n-hexanone, concentration by evaporation	GC/FID	1 ng/mL	72±8%	Kessler et al. 1990
Blood for styrene oxide	Extraction with benzene	GC/MS	10 ng/g	92±21%	Langvardt and Nolan 1991

[a]Unless otherwise designated, analyses are for styrene.
[b]Values were reported for benzene; authors indicated that other VOCs had similar levels of detection
[c]Detection limits were 0.63 µg/mL for mandelic acid, 0.78 µg/mL for phenylglyoxylic acid, and 0.52 µg/mL for hippuric acid.

CV = coefficient of variation; CI = confidence interval; EDTA = ethylene diamine tetra acetic acid; FID = flame ionization detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; MA = mandelic acid; MS = mass spectrometry; PGA = phenylglyoxylic acid; UV = ultraviolet; VOC = volatile organic compound

which accuracy data are available. For example, the most sensitive for styrene detection limits were 0.002 µg/L in water, 4 µg/kg in soil, and 500 µg/kg in solid waste. No significant reports were found pertaining to styrene degradation products in environmental samples. Information on methods for the determination of styrene in environmental samples is summarized in Table 7-2.

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

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. Styrene and its primary metabolites, MA and PGA, can be detected in several human tissues (blood, urine, adipose tissue, and in several organs [Table 7-1]), as well as in exhaled breath. The detection limits range in the parts per billion to parts per trillion range (Ashley et al. 1992; Chambers et al. 2006). Approaches have been developed to provide more efficient and rapid assessment of exposure, such as where the subject breathes for short periods of time into different types of sample collectors (tedlar bags, evacuated canisters, even directly into a mass spectrometer interface [Wallace et al. 1996]), allowing samples to be collected efficiently for subsequent or immediate analysis. Personal monitoring badges containing charcoal have also been developed for longer-term assessment of exposure to styrene and other volatiles, which have been calibrated for comparison to levels detected in the subjects' blood (Romieu et al. 1999).

The concentration of the metabolites, MA and PGA, in urine has been found to correlate with average exposure levels in air (Härkönen et al. 1978), and so may be used as a biomarker of exposure. However,

Table 7-2. Analytical Methods for Determining Styrene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Homogenization, headspace sampling	GC/MS	1 µg/kg	No data	Gilbert and Startin 1983
Air	Retention by activated carbon	GC[a]	No data	No data	ASTM 1988a
Air	Retention by activated carbon, elution with carbon disulfide	GC[b]	No data	No data	ASTM 1988b
Air	Retention by activated carbon, elution with carbon disulfide	HRGC/FID	0.01 mg/sample	No data	NIOSH 1984
Wastewater	Stable isotope dilution method, followed by solvent extraction	GC/MS	10 µg/L	No data	EPA 2001
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax®	GC/PID	0.01 µg/L	96–104%	EPA 1989f
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax®	GC/PID	0.008 µg/L	No data	EPA 1989g
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax®	HRGC/MS	0.20 µg/L	120% (at 1 µg/L)	EPA 1989h
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax®	HRGC/MS	0.04 µg/L	102%	EPA 1989i
Water	Purge and trap with nitrogen or helium	GC/PID	0.01 µg/L	104%	EPA 1995
Water	Purge and trap	GC/PID	0.01 µg/L	104%	EPA 1996
Water	Purge by helium, and trap at low temperature	GC/FID	0.002 µg/L	No data	Miermans et al. 2000
Water	Purge and trap on VOCARB or equivalent	GC/MS	0.039 µg/L	94–110%	USGS 1998
Soil, low level	Purge by helium, collection on solid, thermal desorption	GC/MS	4 µg/kg	No data	EPA 1986c
Solid waste, nonwater miscible	Purge by helium, collection on solid, thermal desorption	GC/MS	500 µg/kg[c]	No data	EPA 1986c

Table 7-2. Analytical Methods for Determining Styrene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Solid waste	Purge by helium, collection on solid, thermal desorption	GC/MS	500 µg/kg[c]	No data	EPA 1986b

[a]Absorption characteristics for sampling atmospheric vapor with activated carbon for subsequent analysis by GC.
[b]Generic method for the determination of organics.
[c]Estimation from detection limits in water.

FID = flame ionization detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry; PID = photoionization detection; UV = ultraviolet

measurements of MA and PGA are not specific for this purpose (Bartolucci et al. 1986) and these metabolites can result from the metabolism of other organic substances, particularly ethylbenzene (Baselt 1988b). Levels of MA and PGA in biological samples from the general population probably are below the detection limits of methods that are currently used (Baselt 1988a). However, it is likely that normal background levels of these metabolites in unexposed individuals are too low to be of any significance. Although new and improved methods for the determination of styrene and its metabolites in biological samples need not have a high priority, additional work on standardization of these methods for use in biological samples accompanied by additional studies involving interlaboratory comparisons of recovery, accuracy, and precision data would be useful.

Clinical means have been proposed to indicate exposure to styrene. In general, these are not sufficiently sensitive, specific, or well characterized. The most common symptom of exposure, impairment of central nervous system function, is not unique to styrene. Neither cytogenetic monitoring of peripheral lymphocytes nor unscheduled DNA synthesis have been sufficiently well characterized as biomarkers of exposure to styrene.

There is currently some information that can be used to correlate levels of biomarkers of exposure to styrene in biological media with adverse health effects. Central nervous system depression has been correlated with a urinary MA concentration of ≥800 mg/L and a decrement in psychomotor performance in association with a concentration of ≥1,200 mg/L (Härkönen et al. 1978). The styrene concentrations in air producing these effects and urinary MA levels were relatively high. Studies to determine if effects at lower levels of exposure could also be correlated to metabolite levels in urine would be valuable. However, the design of studies involving controlled inhalation exposures in humans is precluded by the potential carcinogenicity of styrene.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. In an occupational setting, the medium that is of most concern for human exposure to styrene is air, although at Superfund sites, contaminated groundwater may pose a danger. Methods are well developed for the determination of styrene in water and air with excellent selectivity and sensitivity (ASTM 1988a, 1988b; EPA 1989f, 1989g, 1989i, 1995, 1996; NIOSH 1984; USGS 1998). Methods for the determination of styrene in soil and waste samples are not as well developed and may require additional testing and validation (EPA 1986b, 1986c, 2001).

The detection limits for styrene in environmental media cited in Table 7-2 (0.01 mg/sample, typically 10 L, NIOSH 1984; 0.002 µg/L in water, Miermans et al. 2000; and 4 µg/kg in soil, EPA 1986c) are low enough to enable the determination of styrene in any environmental medium likely to pose a hazard to health based upon information currently available in the literature. These detection limits are probably below most ambient background levels of styrene.

Sampling methodologies for compounds such as styrene pose typical collection problems that include the collection of samples that are nonrepresentative, may be of insufficient sample volume, may contain interfering materials that result in low sample recovery, or may contain interfering contaminating chemicals. Other sampling methods may be labor-intensive, or require tedious extraction and purification procedures (Green and Le Pape 1987; Miermans et al. 2000). Methods that measure organic compounds such as styrene *in situ* in water and other environmental media without the need for sampling and extraction procedures to isolate the analyte prior to analysis are desirable. One such method has been patented, but no commercial products have been identified (see below).

In regard to methods for determining parent styrene and degradation products in environmental media, the following conclusions may be drawn: Because styrene can be detected instrumentally and determined in air and normal water samples with totally adequate selectivity and sensitivity, no additional data are needed at this time. A moderate need exists to improve methodologies to determine styrene in soil, sludges, and solid wastes. Styrene degradation products are a different matter in that little information is available on their determination in environmental samples. In air, these compounds should consist predominantly of photochemical oxidation products, whereas in water and soil samples, they are expected to be biodegradation products. Additional research is needed on the determination of these materials.

7.3.2 Ongoing Studies

No current ongoing studies were found in the Federal Research in Progress database (FEDRIP 2007) regarding the development of analytical methods for the detection of styrene or its metabolites.

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of styrene and other volatile organic compounds in blood. These methods use purge and trap methodology, high-resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

In addition to the detection and identification of styrene using chromatographic means, where current detection limits approach analytical thresholds, other technologies may offer additional routes for detection of styrene in samples, especially for aquatic environmental samples. Immunoassay-based methods of analysis offer rapid analysis times, high sensitivity, and often high selectivity for various organic pollutants and other chemicals of concern. While styrene and its metabolites are considered important chemicals to monitor using such techniques, no known assays have been commercialized, even though one patent has been issued for a method that claims to detect styrene and other VOCs by immunoassay (patent 5,358,851, issued in 1994 [Peck 1994]). No additional information was found regarding the continued development (or use or application) of this technology.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

ATSDR has derived an acute-duration inhalation MRL of 5 ppm for styrene. This MRL is based on a NOAEL of 49 ppm for alterations in tests of reaction time, memory, attention, color discrimination, and olfactory threshold in subjects exposed to styrene for 6 hours (Ska et al. 2003) and an uncertainty factor of 10 to account for human variability.

ATSDR has derived a chronic-duration inhalation MRL of 0.2 ppm for styrene. This MRL is based on a minimal LOAEL of 20 ppm estimated from a meta-analysis of data (Benignus et al. 2005) from occupational exposure studies demonstrating alterations in choice reaction time and color discrimination in styrene workers. The minimal LOAEL was adjusted for intermittent exposure (8 hours/day, 5 days/week) and divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability).

EPA (IRIS 2009) has derived an inhalation reference concentration (RfC) of 1 mg/m^3 (0.2 ppm) based on a $NOAEL_{HEC}$ value of 34 mg/m^3 in a cross-sectional study in workers finding central nervous system effects in workers exposed to >22 ppm (Mutti et al. 1984a) and an uncertainty factor of 30 (3 for the use less than chronic study, 3 for human variability, and 3 for database inadequacies).

ATSDR has derived an acute-duration oral MRL of 0.1 mg/kg/day for styrene. This MRL is based on a LOAEL of 100 mg/kg/day for impaired learning in rats exposed to styrene for 14 days (Husain et al. 1985) and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from rats to humans, and 10 for human variability).

EPA (IRIS 2009) has established an oral reference dose (RfD) of 0.2 mg/kg/day based on a NOAEL of 200 mg/kg/day from a subchronic oral toxicity study in beagle dogs in which red blood cell and liver effects was observed (Quast et al. 1979). The uncertainty factor used in this assessment was 1,000 (10 for interspecies extrapolation, 10 for human variability variation, and 10 for extrapolation of subchronic effects to chronic effects).

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

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

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2006
WHO	Air quality guidelines		WHO 2000
	TWA based on effects other than cancer or odor/annoyance using an averaging time of 1 week	0.26 mg/m^3	
	Based on sensory effects or annoyance reactions, using an averaging time of 30 minutes		
	Detection threshold	0.07 mg/m^3	
	Recognition threshold	0.21–0.28 mg/m^3	
	Guideline value	0.07 mg/m^3	
	Drinking water quality guidelines	0.02 mg/L[b]	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	85 mg/m^3	ACGIH 2008
	STEL (15-minute TWA)	170 mg/m^3	
AIHA	ERPG-1[c]	213 mg/m^3	AIHA 1995
	ERPG-2[c]	1,065 mg/m^3	
	ERPG-3[c]	4,260 mg/m^3	
EPA	AEGL-1[d]		EPA 2007a
	10 minutes	85 mg/m^3	
	30 minutes	85 mg/m^3	
	60 minutes	85 mg/m^3	
	4 hours	85 mg/m^3	
	8 hours	85 mg/m^3	
	AEGL-2[d]		
	10 minutes	980 mg/m^3	
	30 minutes	682 mg/m^3	
	60 minutes	554 mg/m^3	
	4 hours	554 mg/m^3	
	8 hours	554 mg/m^3	

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	AEGL-3[d]		EPA 2007a
	10 minutes[e]	8,094 mg/m^3 (1,862 ppm)	
	30 minutes[e]	8,094 mg/m^3 (1,862 ppm)	
	60 minutes[e]	4,686 mg/m^3 (1,078 ppm)	
	4 hours	1,448 mg/m^3 (333 ppm)	
	8 hours	1,448 mg/m^3 (333 ppm)	
	Level of distinct odor awareness	2.3 mg/m^3 (0.5 ppm)	
EPA	Hazardous air pollutant	Yes	EPA 2007c 42 USC 7412
NIOSH	REL (10-hour TWA)	50 ppm	NIOSH 2005
	STEL (15-minute TWA)	100 ppm	
	IDLH	700 ppm	
OSHA	PEL (8-hour TWA) for general industry	100 ppm	OSHA 2006c 29 CFR 1910.1000, Table Z-2
	Acceptable ceiling concentration	200 ppm	
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift for a maximum duration of 5 minutes in any 3 hours	600 ppm	
	PEL (8-hour TWA) for shipyard industry	100 ppm	OSHA 2006a 29 CFR 1915.1000
	PEL (8-hour TWA) for construction industry	100 ppm	OSHA 2006b 29 CFR 1926.55, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2007b 40 CFR 116.4

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Drinking water standards and health advisories		EPA 2006
	1-day health advisory for a 10-kg child	20 mg/L	
	10-day health advisory for a 10-kg child	2 mg/L	
	DWEL	7 mg/L	
	Lifetime	0.1 mg/L	
	10^{-4} Cancer risk	No data	
	Master Testing List	Yes[f]	EPA 2007d
	National primary drinking water standards		EPA 2003
	MCLG	0.1 mg/L	
	MCL	0.1 mg/L	
	Public health goal	0.1 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	1,000 pounds	EPA 2007e 40 CFR 117.3
c. Food			
FDA	Bottled drinking water	0.1 mg/L	FDA 2006a 21 CFR 165.110
	Food additives permitted for direct addition to food for human consumption	Yes	FDA 2007b 21 CFR 172
	Indirect food additives: adhesives and components of coatings	Yes	FDA 2006b 21 CFR 175
	EAFUS	Yes[h]	FDA 2007a
d. Other			
ACGIH	Carcinogenicity classification	A4[i]	ACGIH 2008
	Biological exposure indices (end of shift at end of workweek)		
	Sum of mandelic acid and phenyl glyoxylic acid in urine	400 mg/g creatinine	
	Styrene in venous blood	0.2 mg/L	
EPA	Carcinogenicity classification	No data	IRIS 2009
	RfC	1 mg/m^3 (0,2 ppm)	
	RfD	0.2 mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes[j]	EPA 2007f 40 CFR 302.4
	Reportable quantity	1,000 pounds	

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Effective date of toxic chemical release reporting	01/01/2000	EPA 2007g 40 CFR 372.65
NTP	Carcinogenicity classification	No data	NTP 2005

[a]Group 2B: possibly carcinogenic to humans
[b]Concentrations of the substance at or below the health-based guideline value may affect the appearance, taste, or odor of the water, leading to consumer complaints (WHO 2004).
[c]ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing other than mild, transient health effects; ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing irreversible or other serious adverse effects; and ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without life-threatening health effects (AIHA 1995).
[d]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects, however, the effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; and AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2007a).
[e]Safety considerations against the hazard of explosion must be taken into account.
[f]Styrene was recommended to the MTL by the U.S. EPA's Office of Pollution Prevention and Toxics on the basis of the SIDS. Styrene was added to the MTL in 1993 and the chemical testing program is currently underway by way of a VTA. The testing needs include health effects, environmental effects, and environmental fate and exposure.
[g]Potential health effects from exposure above the MCL include liver, kidney, or circulatory system problems. Common sources of contaminant in drinking water include discharges from rubber and plastic factories and leaching from landfills (EPA 2003).
[h]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[i]A4: not classifiable as a human carcinogen
[j]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act and 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; DWEL = drinking water equivalent level; 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; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MTL = Master Testing List; 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; SIDS = Screening Information Data Sets; STEL = short-term expsoure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; VTA = Voluntary Testing Agreement; WHO = World Health Organization

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of

the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, 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 Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Styrene
CAS Numbers: 100-42-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 17
Species: Human

Minimal Risk Level: 5 [ ] mg/kg/day [X] ppm

Reference: Ska B, Vyskocil A, Tardif R, et al. 2003. Effects of peak concentrations on the neurotoxicity of styrene in volunteers. Hum Exper Toxicol 22:407-415.

Experimental design: Groups of 24 healthy men (aged 20–50 years) were exposed to 1 ppm (control exposure), 24 ppm, and 24 ppm with four 15-minute exposures to peak concentrations of 49 ppm, 49 ppm, or 49 ppm with four 15-minute exposures to peak concentrations of 98 ppm for 6 hours. The subjects were exposed to each concentration with a 2-week period between each session. The subjects did not have a history of styrene exposure. At the end of the exposure session the subjects were tested for color discrimination (using the Lanthony D-15 desaturated panel), vision contrast, olfactory threshold, simple reaction time, color word stress (response time), symbol digit matching, digit span memory, and continuous tracking. The subjects were also given a questionnaire to assess mood and symptoms.

Effect noted in study and corresponding doses: No significant styrene-related alterations in performance on color discrimination, olfactory threshold, neurobehavioral tests, mood, or subjective symptoms were found.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

A NOAEL of 49 ppm for the lack of alterations in tests of simple reaction time, choice reaction time, memory, or attention.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No, because the subjects were only exposed once for 6 hours; adjusting this NOAEL from intermittent exposure to continuous exposure 0.04 ppm) may result in an overly conservative MRL.

Other additional studies or pertinent information that lend support to this MRL: Exposure to 99 ppm for 7 hours or 376 ppm for 1 hour (Stewart et al. 1968) resulted in eye irritation in experimental subjects; nasal irritation was also reported at 376 ppm. A significant inhibition of the vestibular-oculomotor system was observed in subjects exposed to 87 ppm for 1 hour (Ödkvist et al. 1982). Studies by Stewart et al. (1968) found alterations in tests of balance or coordination in subjects exposed to 376 ppm for 1 hour, but not after exposure to 99 ppm for 7 hours or 216 ppm for 1 hour; the test used in the Stewart et al. (1968) studies is probably less sensitive than those used by Ödkvist et al. (1982). No significant alterations in performance on neurobehavioral tests were observed in subjects exposed to 20 ppm for 3 hours (Seeber et al. 2004).

The available data suggest that the nervous system is the most sensitive target of styrene toxicity following acute-duration inhalation exposure. The lowest LOAEL for a relevant end point in humans is 87 ppm for vestibular impairment in subjects exposed to styrene for 1 hour (Ödkvist et al. 1982). A similar LOAEL (80 ppm) was identified for nasal effects in mice exposed to styrene for 3 days (Cruzan et al. 2001); this effect was not considered suitable as the basis of an MRL. As stated previously, mice appear to have a greater capacity than humans to generate the reactive metabolite, styrene oxide, in the nasal cavity and a lower capacity to detoxify styrene oxide (Green et al. 2001a). The identification of the nervous system as the critical target of toxicity for styrene is supported by a large number of occupational exposure studies. Delays in reaction time have been observed in workers exposed to 21.9–92 ppm (Cherry et al. 1980; Fallas et al. 1992; Gamberale et al. 1976; Jegaden et al. 1993; Mutti et al. 1984a; Tsai and Chen 1996) and vestibular effects have been observed at 18–36 ppm (Calabrese et al. 1996; Möller et al. 1990; Toppila et al. 2006).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Styrene
CAS Numbers: 100-42-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Human

Minimal Risk Level: 0.2 [ ] mg/kg/day [X] ppm

Reference: Benignus VA, Geller AM, Boyes WK, et al. 2005. Human neurobehavioral effects of long-term exposure to styrene: a meta-analysis. Environ Health Perspect 113:532-538.

Experimental design: Benignus et al. (2005) used data from occupational exposure studies examining color vision impairment (Campagna et al. 1996; Eguchi et al. 1995; Gobba et al. 1991; Gong et al. 2002; Kishi et al. 2001) and delays in choice reaction time (Jegaden et al. 1993; Mutti et al. 1984a; Triebig et al. 1989; Tsai and Chen 1996). Average styrene exposure concentrations for each study were estimated from individual data reported in the papers; for studies reporting individual data as urinary mandelic acid levels, standardized methods for converting to styrene exposure levels were used. Cumulative styrene exposure was estimated by multiplying exposure level by length of employment. A common metric of effect magnitude (percentage of baseline) was calculated for the different neurological effects.

Effect noted in study and corresponding doses: A significant linear relationship between choice reaction time and cumulative styrene exposure was found; cumulative exposure accounted for 91% of the variance in reaction time. Similarly, a significant relationship between CCI and cumulative styrene exposure was found, with cumulative exposure accounting for 35% of the variance in CCI. Using the regression equations for these two effects, the investigators estimated that exposure to 150 ppm for 8 work-years would result in a 50% increase in choice reaction time and a 17% increase in CCI score; exposure to 20 ppm for 8 work-years would result in a 6.5% increase in choice reaction time and a 2.23% increase in CCI score. As discussed in Benignus et al. (2005), a 7% decrease in reaction time would prevent 58,000–70,000 injuries per year from automobile accidents. The investigators also noted that CCI increases with age, and the rate of increase is about 10% per 13 years of age; thus, a 2.23% decrease in color perception would be roughly equivalent to 2.9 additional years of age. Based on this analysis, 20 ppm is considered a LOAEL for neurological effects.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

A minimal LOAEL of 20 ppm in the Benignus et al. (2005) meta-analysis was selected as the point of departure for the chronic-duration inhalation MRL. The LOAEL was classified as a minimal LOAEL based on the findings of Triebig et al. (2001) that alterations in color vision were reversible and the workers were not aware of any changes in color vision.

Uncertainty Factors used in MRL derivation: 30

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes.

$LOAEL_{ADJ}$ = 20 ppm x 8 hours/24 hours x 5 days/7 days
$LOAEL_{ADJ}$ = 4.8 ppm

Other additional studies or pertinent information that lend support to this MRL: A large number of occupational exposure studies have examined the toxicity of styrene; however, most of these studies have focused on the potential neurotoxicity of styrene, which appears to be the most sensitive effect. Two common limitations of the occupational exposure studies are: (1) the range of current styrene levels for the workers is typically large and it is difficult to ascribe the observed effects to the mean or median exposure level and (2) historical exposure to higher styrene levels are not adequately taken into consideration. The use of urinary levels of mandelic acid, phenylglyoxylic acid, or mandelic acid plus phenylglyoxylic acid levels as biomarkers for styrene exposure eliminates another common limitation of styrene occupational exposure studies, which is poor characterization of styrene exposure levels due to the lack of personal air samples and the workers' use of respirators with or without canisters.

A variety of neurological effects have been reported in workers at reinforced plastic manufacturing facilities, including decreased color discrimination, slowed reaction time, impaired performance on other neurobehavioral tests, permanent hearing threshold shifts, vestibular effects, altered nerve conduction velocity, and increases in subjective symptoms. A summary of the results of studies for some of these neurological effects is presented in Table A-1 (more details regarding these studies and other studies of neurological effects in styrene workers are presented in Table 3-2). An alteration in color discrimination is one of the more consistently found neurological effects; it may also be one of the more sensitive effects. Color discrimination was typically measured using the Lanthony desaturated panel D-15 test in which the subjects were asked to arrange 15 painted caps in a line with definite chromatic sequence; the TCDS and CCI are used to quantitatively analyze the results. LOAEL values of 6–93 ppm have been identified; however, these LOAELs often reflect the mean exposure level or the lower end of the range of exposure levels. Other neurological effects that have been frequently found include alterations in performance on neurobehavioral tests, particularly reaction time, in workers exposed to ≥21 ppm; vestibular alterations at ≥18 ppm; and increased frequency of clinical symptoms (e.g., tiredness and headaches in workers exposed to ≥6 ppm). Hearing loss and alterations in nerve conduction velocity have also been reported in some studies, but the finding is not consistent across studies.

Table A-1. Results of Selected Human Neurotoxicity Studies

Result	Reference	NOAEL (ppm)	LOAEL (ppm)
Decreased color discrimination	Chia et al. (1994)		6
	Kishi et al. (2001)	4	10
	Gong et al. (2002)		10
	Gobba et al. (1991)		16
	Triebig et al. 2001		20
	Iregren et al. (2005)		22
	Fallas et al. (1992)		24.3
	Campagna et al. (1996)		265
	Eguchi et al. (1995)	8	93
Neurological symptoms	Flodin et al. (1989)	6	
	Edling et al. (1993)	8.6	
	Checkoway et al. (1992)	10.8	18.9
	Cherry et al. 1980		92
Vestibular effects	Möller et al. (1990)		18
	Toppila et al. (2006)		24.8
	Calabrese et al. (1996)		36
Reaction time	Edling et al. (1993)	8.6	21.9
	Tsai and Chen (1996)		21.9
	Jegaden et al. (1993)		22.68
	Fallas et al. (1992)		24.3
	Mutti et al. (1984a)		25
	Gamberale et al. (1976)		4,755
	Cherry et al. (1980)		92

Non-neurological effects observed in styrene workers include obstructive lung effects (Chmielewski and Renke 1975), mild hematological alterations (Checkoway and Williams 1982; Stengel et al. 1990; Thiess and Friedheim 1978), and impaired immune response to concanavalin (Somorowská et al. 1999; Tulinska et al. 2000). Although exposure levels were not reported in all of these studies, effects were typically observed at styrene concentrations of >20 ppm. Clinical chemistry studies did not find alterations indicative of impaired liver (Härkönen et al. 1984; Hotz et al. 1980; Lorimer et al. 1978; Thiess and Friedheim 1978) or kidney (Verplanke and Herber 1998; Viau et al. 1987; Vyskocil et al. 1989) function in workers exposed to ≥24 ppm.

Chronic-duration studies in laboratory animals identify the nasal olfactory epithelium as the most sensitive end point. Atrophic and/or degenerative changes were observed in rats exposed to 50 ppm styrene 6 hours/day, 5 days/week for 104 weeks (Cruzan et al. 1998) and respiratory metaplasia in the nasal olfactory epithelium were observed in mice exposed to 20 ppm 6 hours/day, 5 days/week for 98–104 weeks (Cruzan et al. 2001). As noted previously, mice do not appear to be a good model for potential respiratory effects in humans.

In addition to the studies included in the Benignus et al. (2005) meta-analysis, a LOAEL of 20 ppm is supported by a color discrimination study conducted by Triebig et al. (2001). In this study, significant

increases in CCI values were observed in styrene workers with urinary mandelic acid plus phenylglyoxylic acid levels of ≥472 mg/g creatinine (approximately 20 ppm air styrene concentration), when compared to >95th percentile age-dependent reference CCI values. An advantage of the Triebig et al. (2001) study is that individual exposure and CCI data were reported, which diminishes the problem of ascribing an observed effect to the mean or median concentration and the study addresses the issue of biological relevance because the CCI scores were compared to the 95th percentile of age-dependent reference values rather than values in the control group.

In comparisons between styrene workers and a control group employed at the same facility without styrene exposure, Triebig et al. (2001) found no significant differences in CCI scores between workers and controls when the tests were conducted on a Monday morning, but CCI scores were significantly different when measured on a Thursday afternoon. Within the styrene-exposed workers, CCI scores on Monday morning and Thursday afternoon were not significantly different. After a 4-week nonexposure period, the CCI scores were significantly reduced in the styrene workers. After styrene exposure levels were lowered, no difference between workers and controls was observed on Monday morning or Thursday afternoon. However, among styrene workers, there were significant differences between Monday morning and Thursday afternoon measurements and between Monday morning and post-vacation levels. These findings provide suggestive evidence that the alterations in color discrimination were reversible.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Styrene
CAS Numbers: 100-42-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 3
Species: Rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: Husain R, Srivastava SP, Seth PK. 1985. Some behavioral effects of early styrene intoxication in experimental animals. Arch Toxicol 57:53-55.

Experimental design: Groups of 15 male Wistar rats were administered by gavage 0, 100, or 200 mg/kg/day styrene in ground nut oil for 14 consecutive days. Spontaneous motor activity for a period of 10 minutes was measured 24 hours after the last dose. After baseline activity was measured, the rats received an intraperitoneal injection of 2.5 mg/kg amphetamine, and amphetamine-induced spontaneous motor activity was measured. Two days after exposure termination, acquisition training was initiated using a Cook's pole climbing apparatus. Learning was assessed by measuring the number of times the rat climbed the pole after the conditioned stimulus to avoid the foot-shock unconditioned stimulus. The rats were tested for 4 days. Noradrenaline, dopamine, and serotonin levels were measured in seven regions of the brain in six rats/group killed after the acquisition training.

Effect noted in study and corresponding doses: No overt signs of toxicity were observed. No significant alterations in locomotor activity were observed with or without amphetamine induction. Significantly greater increases in percent avoidance response (indicative of impaired learning) were observed at 100 and 200 mg/kg/day; no difference was found between the two styrene groups. The effects were observed on test days 3 and 4. Significant increases in the level of serotonin in the hypothalamus (70%), hippocampus (51%), and midbrain (29%) were observed at 200 mg/kg/day. Styrene did not affect brain noradrenaline and dopamine levels.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

A LOAEL of 100 mg/kg/day for impaired learning

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

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

Other additional studies or pertinent information that lend support to this MRL: A limited number of studies have examined the acute toxicity of orally-administered styrene; these studies have examined potential neurotoxicity and developmental toxicity. No developmental effects were observed in rats administered a single dose of 300 mg/kg on gestational day 11 (Daston et al. 1991) or administered 300 mg/kg/day (administered as two daily doses of 150 mg/kg) on gestational days 6–15 (Murray et al. 1978). Impaired learning was observed in rats administered via gavage 100 or 200 mg/kg/day for 14 days (Husain et al. 1985); increases in serotonin levels in the hypothalamus, hippocampus, and midbrain were also observed at 200 mg/kg/day. In another study, increases in dopamine receptor binding was observed in rats administered a single gavage dose of 200 mg/kg (Agrawal et al. 1982).

Although there is a limited acute toxicity database, longer-term oral studies support the selection of neurotoxicity as the principal effect. The lowest LOAEL identified for a systemic effect is 400 mg/kg/day for Heinz body formation in dogs administered styrene by gavage for 561 days (Quast et al. 1979); the identified NOAEL was 200 mg/kg/day. Decreased spermatozoa counts were observed in adult rats administered 400 mg/kg 6 days/week for 60 days (Srivastava et al. 1989), young rats exposed via lactation on postnatal days 1–21 (maternal dose of 400 mg/kg/day) (Srivastava et al. 1992a), and young rats administered 200 mg/kg 6 days/week on postnatal days 1–61 (Srivastava et al. 1992b); the NOAELs identified in these three studies were 200, 200, and 100 mg/kg, respectively. Marked degeneration of the seminiferous tubules was also observed in the adult rats administered 400 mg/kg (Srivastava et al. 1989). Impaired learning was also observed in rats administered 500 mg/kg 5 days/week for 8 weeks (Bushnell 1994); a NOAEL was not identified in this study. The extensive inhalation toxicity database for styrene also supports the selection of neurotoxicity as the most sensitive target of toxicity; both the acute- and chronic-duration inhalation MRLs are based on neurological effects in humans. Neurological effects observed in chronically exposed styrene workers include decreased color discrimination, slowed reaction time, increased prevalence of neurological symptoms, and ototoxicity (hearing and vestibular effects).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

SAMPLE

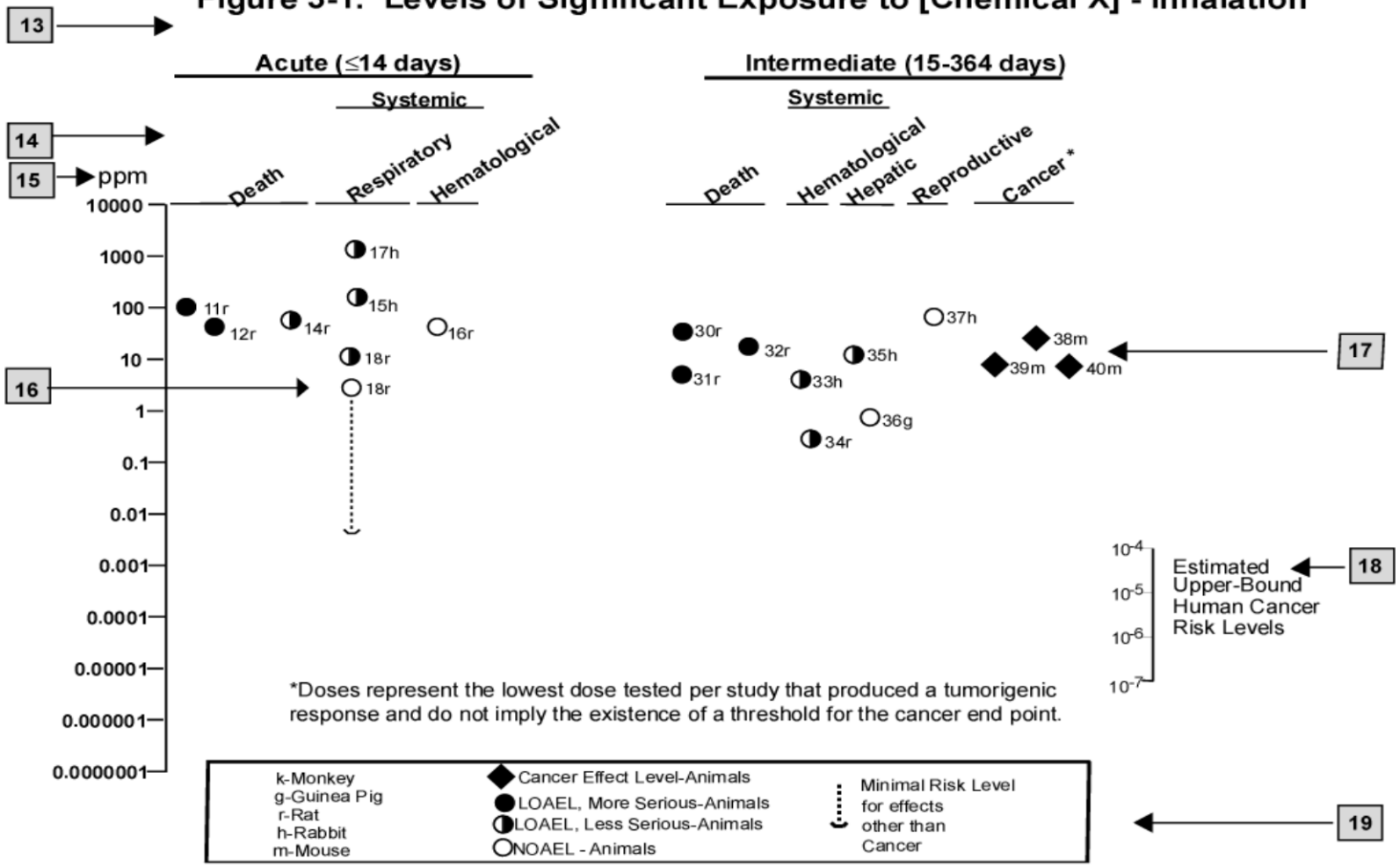
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
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 $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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

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APPENDIX D. INDEX