TOXICOLOGICAL PROFILE FOR ETHYLBENZENE

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Ethylbenzene, 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:

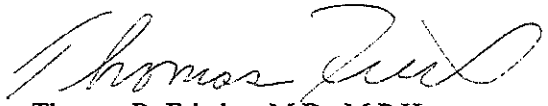
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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 ethylbenzene. The panel consisted of the following members:

Draft for Public Comment:

1. John DeSesso, Ph.D., Senior Fellow, Noblis, Falls Church, VA;

2. James McDougal, Ph.D., Professor and Director of Toxicology Research, Boonshoft School of Medicine, Wright State University, Department of Pharmacology and Toxicology, Dayton, OH;

3. Andrew Salmon, Ph.D., Senior Toxicologist and Chief, Air Toxicology and Risk Assessment Unit, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA.

Revised Minimal Risk Levels:

4. John DeSesso, Ph.D., Senior Fellow, Noblis, Falls Church, VA;

5. Brent Finley, Ph.D., DABT, Principal Health Scientist and Vice President, ChemRisk, San Francisco, CA;

6. Andrew Salmon, Ph.D., Senior Toxicologist and Chief, Air Toxicology and Risk Assessment Unit, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA.

These experts collectively have knowledge of ethylbenzene'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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CONTENTS

LIST OF FIGURES

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LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about ethylbenzene 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. Ethylbenzene has been found in at least 829 of the 1,689 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 ethylbenzene 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 ethylbenzene, 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 ETHYLBENZENE?

Colorless liquid that smells like gasoline	You can smell ethylbenzene in the air at 2 parts of ethylbenzene per million parts of air (2 ppm). It evaporates at room temperature and burns easily.

Used in industry and in consumer products	Ethylbenzene is found naturally in oil. Large amounts of ethylbenzene are produced in the United States, most of which is used to make styrene. Ethylbenzene is also used in fuels and solvents. Consumer products containing ethylbenzene include: • gasoline • paints and inks • pesticides • carpet glues • varnishes and paints • tobacco products • automotive products

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

1.2 WHAT HAPPENS TO ETHYLBENZENE WHEN IT ENTERS THE ENVIRONMENT?

Most commonly found in air	Ethylbenzene moves easily into the air from water and soil. Ethylbenzene in soil can also contaminate groundwater.
Rapidly broken down in air	Air: Ethylbenzene in air is broken down in less than 3 days with the aid of sunlight. Water: In surface water such as rivers and harbors, ethylbenzene breaks down by reacting with other compounds naturally present in water. Soil: In the soil, ethylbenzene is broken down by soil bacteria.

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

1.3 HOW MIGHT I BE EXPOSED TO ETHYLBENZENE?

Air	If you live in a city or near many factories or heavily traveled highways, you may be exposed to ethylbenzene in the air. Releases of ethylbenzene into the air occur from burning oil, gas, and coal and from industries using ethylbenzene. The median levels of ethylbenzene in air are: • 0.62 ppb in city and suburban locations • 0.01 ppb in rural locations • 1 ppb in indoor air

Water	Ethylbenzene is infrequently detected in private and public groundwater wells used for drinking water. Higher levels of ethylbenzene may be found in private residential wells near landfills, waste sites, or leaking underground fuel storage tanks. People with ethylbenzene-contaminated tap water could be exposed by drinking the water or eating foods prepared with it. Exposure could also result from breathing in ethylbenzene while showering, bathing, or cooking with contaminated water.
Soil	Background levels in soils have not been reported. Ethylbenzene may get into the soil by gasoline or other fuel spills and poor disposal of industrial and household wastes.
Workplace air	Gas and oil workers may be exposed to ethylbenzene either through skin contact or by breathing ethylbenzene vapors. Varnish workers, spray painters, and people involved in gluing operations may also be exposed to high levels of ethylbenzene. Exposure may also occur in factories that use ethylbenzene to produce other chemicals.
Consumer products	You might be exposed to ethylbenzene by using any of the following products: • gasoline • carpet glues • varnishes and paints • tobacco products • automotive products

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

1.4 HOW CAN ETHYLBENZENE ENTER AND LEAVE MY BODY?

Rapidly enters your body	When you breathe air containing ethylbenzene, it enters your body rapidly and almost completely through your lungs. Ethylbenzene in food or water may also rapidly and almost completely enter your body through the digestive tract. It may enter through your skin when you come into contact with liquids containing ethylbenzene.
Typically leaves your body within 2 days	Once in your body, ethylbenzene is broken down into other chemicals. Most of these other chemicals leave your body in the urine within 2 days. Small amounts of ethylbenzene can also leave your body through the lungs and in feces.

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

1.5 HOW CAN ETHYLBENZENE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed

The effect of ethylbenzene on human health depends on how much ethylbenzene is present, how you are exposed to it, and the length of exposure.

Short-term exposure in air	Humans: Exposure to high levels of ethylbenzene in the air for short periods can cause eye and throat irritation. Exposure to higher levels can result in vertigo and dizziness. Animals: Exposure to very high levels (about 2 million times the usual level in urban air) can cause death.
Long-term exposure in air	Hearing: Exposure to relatively low concentrations of ethylbenzene for several days to weeks resulted in potentially irreversible damage to the inner ear and hearing of animals. Kidney: Exposures to relatively low concentrations of ethylbenzene for several months to years caused in kidney damage in animals. Reproduction: There is no clear evidence that ethylbenzene affects fertility. Cancer: An increase in kidney tumors in rats and lung and liver tumors in mice were found after they were exposed to ethylbenzene in air for 2 years. The International Agency for Research on Cancer (an expert group that is part of the World Health Organization) has determined on that long-term exposure to ethylbenzene may cause cancer in humans.
Long-term exposure by ingestion	Hearing: Rats exposed to large amounts of ethylbenzene by mouth had severe damage to the inner ear.
Short-term eye and skin contact	Irritation: Liquid ethylbenzene caused eye damage and skin irritation in rabbits.

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

1.6 HOW CAN ETHYLBENZENE AFFECT CHILDREN?

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

Children are likely to have similar effects as adults	No information is available about the effect of exposure to ethylbenzene on children. It is likely that children would show the same health effects as adults. We do not know whether children will have effects at the same exposure levels as adults. In immature animals, exposure to inhaled ethylbenzene produced small decreases in weight gain.
Birth defects	We do not know whether ethylbenzene causes birth defects in people. Minor birth defects and low birth weights have occurred in newborn animals whose mothers were exposed air contaminated with ethylbenzene.
Exposure from breast milk	We do not know whether ethylbenzene can accumulate in breast milk.

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

Limit children's exposure to consumer products containing ethylbenzene	Use adequate ventilation to minimize exposure to ethylbenzene vapors from consumer products such as • gasoline • pesticides • varnishes and paints • newly installed carpeting • automotive products Sometimes older children sniff household chemicals in an attempt to get high. Your children may be exposed to ethylbenzene by inhaling products containing it, such as paints, varnishes, or gasoline. Talk with your children about the dangers of sniffing chemicals.
Store household chemicals out of reach of young children	Always store household chemicals in their original labeled containers out of reach of young children to prevent accidental poisonings. Never store household chemicals in containers children would find attractive to eat or drink from, such as old soda bottles. Gasoline should be stored in a gasoline can with a locked cap.
Follow directions on label	Always follow directions on household products (for example, use only with adequate ventilation.)
Limit exposure to tobacco smoke	Ethylbenzene is a component of tobacco smoke. Avoid smoking in enclosed spaces such as inside the home or car in order to limit exposure to children and other family members.

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

Can be measured in blood and breath	Ethylbenzene can be measured in blood and in the breath of people exposed to ethylbenzene. This should be done within a few hours after exposure occurs because these metabolites leave the body very quickly.
Metabolites can be measured in urine	The presence of ethylbenzene breakdown products (metabolites) in urine might indicate that you were exposed to ethylbenzene; however, these breakdown products can also form when you are exposed to other substances, such as styrene. The detection of these metabolites in your urine cannot be used to predict the kind of health effects that might develop from that exposure. You should have this test done within a few hours after exposure occurs because these metabolites leave the body very quickly.

For more information on the different substances formed by ethylbenzene breakdown and on tests to detect these substances in the body, see 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, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that 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 ethylbenzene include the following:

Levels in drinking water set by EPA	The EPA has determined that exposure to ethylbenzene in drinking water at concentrations of 30 ppm for one day or 3 ppm for 10 days is not expected to cause any harmful effects in a child. The EPA has determined that lifetime exposure to 0.7 ppm ethylbenzene is not expected to cause any harmful effects.
Levels in surface water set by EPA	If you eat fish and drink water from a body of water, the water should contain no more than 0.53 ppm ethylbenzene.
Levels in workplace air set by OSHA	OSHA set a legal limit of 100 ppm ethylbenzene 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 ETHYLBENZENE IN THE UNITED STATES

Ethylbenzene is widely distributed in the environment. It is primarily used for the production of styrene, which is the monomeric unit for polystyrene materials. Ethylbenzene is also used as a solvent and in the manufacture of several organic compounds other than styrene; however, these uses are very minor in comparison to the amounts used for styrene production. The production volume of ethylbenzene is typically among the highest of all chemicals manufactured in the United States. In 2005, nearly 12 billion pounds of ethylbenzene were produced domestically, with historical levels ranging anywhere from approximately 7 to 13 billion pounds annually. Routine human activities, such as driving automobiles, boats, or aircraft, and using gasoline powered tools and equipment as well as paints, varnishes, and solvents release ethylbenzene to the environment. Environmental and background levels of ethylbenzene are generally small and therefore, have minimal impact on public health. Trace levels of ethylbenzene are found in internal combustion engine exhaust, food, soil, water, and tobacco smoke, but usually at levels well below those that have been shown to exhibit toxic effects in laboratory animals or human exposure studies.

Ethylbenzene is not considered highly persistent in the environment. It partitions primarily to air and removal via photochemically generated hydroxyl radicals is an important degradation mechanism. The half-life for this reaction in the atmosphere is approximately 1–2 days. Biodegradation under aerobic conditions and indirect photolysis are important degradation mechanisms for ethylbenzene in soil and water. Based on a vapor pressure of 9.53 mm Hg and Henry's law constant of 7.9×10^{-3} atm-m^3/mol, volatilization from water and soil surfaces is expected to be an important environmental fate process for ethylbenzene. If released to soil, ethylbenzene is expected to possess moderate mobility based on a soil adsorption coefficient (K_{oc}) value of 240.

Ethylbenzene is ubiquitous in ambient air, primarily as a result of automobile emissions. The median level of ethylbenzene in city and suburban air was reported as 2.7 μg/m^3 (0.62 ppb). In contrast, the median level of ethylbenzene measured in rural locations was 0.056 μg/m^3 (0.013 ppb). Ethylbenzene levels in indoor air tend to be higher than corresponding levels monitored in outdoor air, as a result of contributions from environmental tobacco smoke (ETS) and various consumer products, in addition to the permeation indoors of ethylbenzene from attached garages or outside air. One study analyzed the components of ETS for the 50 top-selling U.S. cigarette brand styles in 1991 and for the University of

Kentucky Research cigarette, K1R4F. The ethylbenzene concentrations measured were 8.68 μg/m^3 for full-flavor cigarettes, 8.24 μg/m^3 for full-flavor, low-tar cigarettes, and 8.72 μg/m^3 for ultra-low-tar cigarettes. The mean ethylbenzene concentration for all cigarettes was 8.50 μg/m^3. One study reported a maximum outdoor air concentration of 7.4 μg/m^3 (1.7 ppb) for ethylbenzene at four residential locations, while indoor air concentrations at these same homes ranged from 5 to 110 μg/m^3 (1–25.3 ppb). Ethylbenzene is also released to the air during processing of crude oil.

Ethylbenzene is detected infrequently in surface water. Data from the EPA STOrage and REtrieval Database (STORET), indicated that ethylbenzene was detected in <3% of the surface water samples analyzed in the United States from January 2005 to March 2007, with a maximum concentration of 2 ppb. Ethylbenzene can also be present in groundwater, particularly near current or former landfills, hazardous sites, or gas stations. Oil- and gasoline-contaminated sites have also been found to have relatively high ethylbenzene concentrations in soil.

Ethylbenzene was identified in 82 different food items at a maximum concentration of 0.129 ppm in data obtained from the FDA Total Diet Study Market Basket Surveys collected between September 1991 and October 2003. Trace concentrations of ethylbenzene have been reported in split peas (0.013 mg/kg [ppm]), lentils (0.005 mg/kg [ppm]), and beans (mean concentration 0.005 mg/kg [ppm]; maximum concentration 0.011 mg/kg [ppm]).

The general population is primarily exposed to ethylbenzene from the inhalation of ambient air. This is due to the direct release of ethylbenzene into the air by the burning of fossil fuels or industrial processes, and partitioning into the air from other media (e.g., soil, surface water). This partitioning of ethylbenzene into the air or water would play a role in exposure to populations living near hazardous waste sites. In addition to inhalation exposure, ingestion of ethylbenzene may also occur because trace amounts have been found in water supplies and various food items.

2.2 SUMMARY OF HEALTH EFFECTS

In humans, eye irritation was observed after exposure to 10,000 ppm ethylbenzene for a few seconds. Volunteers reported irritation and chest constriction after acute-duration exposures to 2,000 ppm ethylbenzene. These symptoms worsened as the concentration was increased to 5,000 ppm. Human exposures in the range of 2,000–5,000 ppm ethylbenzene were associated with dizziness and vertigo. Complete recovery occurs if exposure is not prolonged. Momentary ocular irritation, a burning sensation,

and profuse lacrimation were observed in humans exposed to 1,000 ppm ethylbenzene. Workers exposed occupationally to solvent mixtures that included ethylbenzene showed an increased incidence of hearing loss compared to unexposed individuals. Respiratory effects were not observed in two patients exposed to 55.3 ppm ethylbenzene for 15 minutes. An increase in the mean number of lymphocytes and a decrease in hemoglobin levels were observed during a 1-year period in workers exposed chronically to solvents including ethylbenzene. However, no adverse hematological effects were observed in workers exposed to ethylbenzene for 20 years. Although no information on ethylbenzene concentrations was reported, an estimated concentration of 6.4 mg/m^3 was derived from a mean post-shift in urinary mandelic acid concentration in workers, based on the relationship between ethylbenzene concentrations in air and urinary mandelic acid concentration in a chamber-exposed group. No liver lesions or differences in liver function tests between exposed and nonexposed workers were observed and no cases of malignancy in workers were reported. However, given the low exposure concentration, this study had limited the power to detect any effect. No other studies in humans exposed to ethylbenzene were located. Given that little data in humans are available, it is assumed that adverse effects observed in animals are relevant to humans.

Acute-duration and intermediate-duration studies in animals suggest that the auditory system is a sensitive target of ethylbenzene toxicity. Significant losses of outer hair cells (OHCs) in the organ of Corti have been observed in rats after acute-duration exposure ≥400 ppm and intermediate-duration inhalation exposure to ≥200 ppm ethylbenzene. These OHC losses have been observed up to 11 weeks after termination of the exposure, suggesting that these effects may be irreversible. Significant deterioration of auditory thresholds is also observed in animals affected with OHC losses. Auditory deficits have also been observed in animals after an intermediate-duration oral exposure to ethylbenzene. An almost complete loss of the three rows of outer hair cells in the organ of Corti was observed in rats 10 days after the last dose (900 mg/kg/day) in an acute-duration study. Effects on the central nervous system, such as moderate motor activation, narcotic effects, changes in posture and arousal, and salivation and prostration have been observed in animals after acute- and intermediate-duration exposure to ≥400 ppm ethylbenzene.

Results of 4- and 13-week studies indicate that intermediate-duration oral exposure to ethylbenzene produces effects to the liver. Effects indicative of liver toxicity observed included increased activity of serum liver enzymes (alanine aminotransferase and γ-glutamyl transferase) in males (≥250 mg/kg/day) and females (750 mg/mg/day), increased absolute and relative liver weights (≥250 mg/kg/day in males and females), and a dose-related increase in the incidence of centrilobular hepatocyte hypertrophy

(≥250 mg/kg/day in males and females). Increased bilirubin (≤250 mg/kg/day in males and 750 mg/kg/day in females), total protein (750 mg/kg/day in females), albumin (750 mg/kg/day in males and females), globulins (750 mg/kg/day in females), and cholesterol (≤250 mg/kg/day in males and females), and decreased prothrombin time (750 mg/kg/day in males and ≥250 mg/kg/day in females) were considered by study investigators as adaptive effects in the liver. In males in the 75 mg/k/day group, relative liver weight was significantly increased by 4% compared to controls; however, no histopathological changes, or increases in absolute liver or serum liver enzyme activities were observed at this dosage. Given that ethylbenzene is a microsomal enzyme inducer, and the absence of histopathology and other evidence of liver injury at the 75 mg/kg/day dosage, the small increase in relative liver weight in male rats was at this dosage not considered evidence for an adverse effect on the liver. Results of the 4-week gavage study in rats were similar to those of the 13-week study, identifying no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of 250 and 750 mg/kg/day, respectively, for liver effects. Observed effects consistent with hepatotoxicity included increased absolute and relative liver weights (≥250 mg/kg/day in males and 750 mg/kg/day in females), increased incidence of hepatocyte centrilobular (≥250 mg/kg/day in males and 750 mg/kg/day in females), and increase serum liver enzyme activity (alanine aminotransferase) (750 mg/kg/day in males and females). Histopathological changes characterized by cloudy swelling of parenchymal cells of the liver and an increase in liver weight were observed in female rats administered 408 mg/kg/day by gavage for 6 months. No other hepatic changes were reported. No liver effects were observed in female rats administered 136 mg/kg/day. However, this study was poorly reported and did not provide adequate descriptions of study methods or results.

Guinea pigs exposed to sublethal concentrations of ethylbenzene (≤10,000 ppm for <100 minutes) showed “moderate” pulmonary edema and congestion. These findings had disappeared in animals after a 4–8-day recovery period, suggesting that these pathological effects in the lung are reversible. A 50% respiratory depression was observed in mice exposed to ≥1,432 ppm for 5–30 minutes. Respiratory depression has not been reported in humans exposed to ethylbenzene. Nasal and eye irritation was evident in animals exposed to 1,000 ppm for ≥3 minutes. An NTP study did not observe weight or histopathological effects in the lungs of rats or mice exposed to 782 ppm or rabbits exposed to 1,610 ppm ethylbenzene for 4 weeks. Absolute and relative lung weight was increased in rats, but not mice, exposed to ≥250 ppm for 13 weeks; no treatment-related histopathological effects were observed. Another study did not report pulmonary injury in rats, guinea pigs, rabbits, or monkeys exposed to 600–2,200 ppm ethylbenzene for approximately 6 months; however, only two animals were used in some of the dose groups in rabbits and monkeys. In the NTP study, no treatment-related histopathological effects were

noted in respiratory tissue in rats or female mice exposed to up to 750 ppm ethylbenzene for 2 years. Although an increase in alveolar epithelial hyperplasia was noted in male mice in the 750-ppm group the incidence fell within historical controls for the conducting laboratory. The available data on adverse respiratory effects associated with ethylbenzene exposure in animals and the limited data available in humans suggest that respiratory effects in humans could result following inhalation exposure to high concentrations of ethylbenzene. Respiratory effects from low-level exposure, such as that found in the outdoor air, appear to be less likely.

Developmental effects have been reported in the offspring of pregnant animals exposed to ethylbenzene during gestation. The best reported studies available suggest that developmental effects are generally observed at concentrations of approximately ≥1,000 ppm. Significant increases in the incidence of fetal skeletal variations were observed in the offspring of pregnant rats exposed to 2,000 ppm and reductions in fetal body weight were observed in the offspring of pregnant rats exposed to ≥1,000 ppm ethylbenzene during gestation. Maternal toxicity, manifested as reduced body weight gain, was also observed in rats exposed to ≥1,000 ppm. No developmental effects were observed at concentrations of ≤500 ppm. In contrast, an increased incidence of fetuses with extra ribs was observed in the offspring of rats exposed to 100 ppm during gestation, but not when the animals were exposed to 100 ppm during pre-mating and gestation. No other significant increases in major malformations or minor anomalies were observed. Neurodevelopmental assessments conducted on F2 rat offspring indicated no effects in a functional observational battery assessment, fore- or hind-limb grip strength, swimming ability, motor activity, startle response, or learning and memory assessments at 500 ppm.

The number of implantations or live fetuses per litter and the percentage of resorptions or non-live implants per litter were unaffected in pregnant rats exposed to 2,000 ppm ethylbenzene during gestation. In a two-generation study, estrous cycle length was significantly reduced in F0, but not F1, females exposed to 500 ppm or in rats or mice exposed to 975 ppm ethylbenzene for 90 days. Reproductive parameters were not affected in F0 or F1 males or females at 500 ppm ethylbenzene. Exposure of rats and rabbits to 100 or 1,000 ppm ethylbenzene for 3 weeks during prior to mating or gestation or both resulted in no conclusive evidence of reproductive effects in either species. Assessments of reproductive organs conducted following intermediate- and chronic-duration exposure to ethylbenzene have not observed histopathological changes in the testes of rats, mice, or rabbits exposed to concentrations as high as 2,400 ppm ethylbenzene for 4 days or in rats or mice exposed to 782 ppm ethylbenzene or rabbits exposed to 1,610 ppm for 4 weeks. No effect was observed on spermatid counts, sperm motility, weight of the caudal epididymis, or testicular morphology in rats or mice exposed to 975 ppm ethylbenzene for

90 days. No adverse histopathological effects were seen in the testes of rats or guinea pigs exposed to concentrations up to 1,250 or 600 ppm, respectively, for 6–7 months.

Other systemic effects have been observed in animals after acute-, intermediate-, and chronic-duration exposures to ethylbenzene. Eye irritation and lacrimation have been observed after acute-duration exposures in rats, mice, and guinea pigs exposed to ≥1,000 ppm ethylbenzene. Lacrimation was observed in rats exposed to 382 ppm for 4 weeks. In contrast, no ocular effects were seen in rats or mice after a 13-week exposure to 975 ppm ethylbenzene. Mild irritation, reddening, exfoliation, and blistering have been reported in rabbits when ethylbenzene was applied directly on the skin. Slight irritation of the eye and corneal injuries were observed in rabbits when ethylbenzene was instilled onto the eyes.

One study examined the possible association between occupational exposure to ethylbenzene and increased cancer risk; no cases of malignancy were observed in workers exposed to ethylbenzene for 20 years. Animal studies have found increased incidences of neoplasms in rats and mice following inhalation or oral exposure, which are considered relevant to humans. The inhalation studies conducted by NTP found clear evidence of carcinogenic activity in male rats based on increased incidences of renal tubule neoplasm's and testicular adenomas, some evidence of carcinogenic activity in female rats based on increased incidences of renal tubule adenomas, some evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms, and some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular neoplasms. In a reevaluation of the histopathology of rat kidneys from the NTP study, another study confirmed the NTP findings and suggested that the increased incidence of kidney tumors in rats in the high-dose group was related to a chemical-induced exacerbation of chronic progressive nephropathy (CPN) with a minor contributing factor in male rats being $\alpha_{2\mu}$-globulin nephropathy. The author suggests that since CPN is an age-related disease of rodents without a counterpart in humans, the kidney results of the NTP study are not relevant to humans for risk assessment purposes. However, in an analysis of the association between CPN and renal tubule cell neoplasms in male F344 rats, it was concluded that the association between CPN and renal tubule cell neoplasms is marginal. Results of this analysis suggest that the number of renal tubule cell neoplasms secondary to CPN would be few. An increase in the total number of malignant tumors was observed in rats orally exposed to ethylbenzene; however, data on specific tumor types were not provided. On the basis of the NTP study, IARC has classified ethylbenzene as a Group 2B carcinogen (possibly carcinogenic to humans). In the most recent carcinogenicity assessment by the EPA conducted in 1991, ethylbenzene was classified as Group D (not classifiable as to human carcinogenicity) due to the lack of

animal bioassays and human studies; however, the EPA assessment predated the NTP study. Ethylbenzene is not included in the DHHS's 11th Report on Carcinogens.

Acute- and intermediate-duration studies provide strong evidence that ototoxicity is a sensitive effect following inhalation exposure to ethylbenzene. A more detailed discussion of this effect follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other effects.

A study of workers exposed occupationally to solvent mixtures that include ethylbenzene (mean exposure level 1.8 ppm) showed a 58% incidence of hearing loss compared to 36% in the reference (unexposed) group. The role of ethylbenzene in the observed losses cannot be ascertained from this study given that ethylbenzene was only one of several solvents, most of which were present at mean concentrations 1.5–3.5 times higher than ethylbenzene. Consistent with the outcome of occupational studies showing hearing loss, significant and persistent adverse auditory effects have been shown in animals after acute- and intermediate-duration inhalation exposures to ethylbenzene and after acute-duration oral exposures. OHCs in the organ of Corti (located in the cochlea) are a sensitive target of toxicity of ethylbenzene. Significant losses of OHCs in the organ or Corti were observed in male rats after acute-duration inhalation exposure to ≥400 ppm and intermediate-duration inhalation exposure to ≥200 ppm ethylbenzene. These losses in OHC were observed 8–11 weeks after the last exposures. Inhalation of ≥400 ppm ethylbenzene for 5 days or 4 weeks also resulted in a significant deterioration of auditory thresholds. The magnitude of the shifts in auditory thresholds observed after the first 4 weeks of exposure did not change during a 13-week exposure period or after an 8-week post-exposure recovery period. Inner hair cells were affected by ethylbenzene only at ≥600 ppm in the intermediate-duration study. Guinea pigs exposed to ethylbenzene at 2,500 ppm for 5 days did not show auditory deficits or losses in outer hair cells, whereas significant deficits and hair cell loss were observed in rats exposed to ethylbenzene at 550 ppm. An almost complete loss of OHC was reported in male rats 10 days after an acute-duration oral exposure to ethylbenzene. The mechanisms of the species differences between rats and guinea pigs are not understood. However, given the observations of hearing loss in workers exposed to 1.8 ppm ethylbenzene, the rat appears to be an appropriate animal model.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for ethylbenzene. 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 1990a), 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

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

There is limited information on the acute toxicity of ethylbenzene in humans. Acute exposures to ≥1,000 ppm resulted in ocular irritation, a burning sensation, and profuse lacrimation (Cometto-Muniz and Cain 1995; Thienes and Haley 1972; Yant et al. 1930). Volunteers exposed to 2,000 ppm reported irritation and chest constriction with worsening symptoms when the concentration was increased to 5,000 ppm (Yant et al. 1930). Studies in laboratory animals identify ototoxicity as the most sensitive end point for acute-duration inhalation exposure to ethylbenzene. Damage to the outer hair cells (OHCs) of the organ of Corti and, in some cases, significant reductions in auditory thresholds were observed in rats exposed to ≥400 ppm ethylbenzene by inhalation for 5 days (Cappaert et al. 1999, 2000, 2001, 2002). Loss of OHCs appeared to be concentration-related as losses were 52–66% in animals exposed to 800 ppm ethylbenzene (Cappaert et al. 1999), 40–75% at 550 ppm, and approximately 25% at 400 ppm (Cappaert et al. 2000, 2001). OHC losses in rats exposed to 300 ppm were small (12%) and not statistically significant (Cappaert et al. 2000). Auditory thresholds in rats exposed to ethylbenzene at ≥400 ppm were significantly affected in the mid-frequency region; however, an increasingly broader range of frequencies was affected with increasing concentrations of ethylbenzene (Cappaert et al. 1999, 2000). Auditory assessments indicate that effects were evident shortly after exposure and persisted for up

to 11 weeks (termination of the observation period) (Cappaert et al. 1999, 2000, 2001, 2002), suggesting that the auditory effects might be irreversible. Cappaert et al. (2002) demonstrated a significant species difference in the susceptibility of rats and guinea pigs to the ototoxic effects of ethylbenzene, with guinea pigs showing no auditory deficits or losses in OHCs at 2,500 ppm ethylbenzene after 5 days (Cappaert et al. 2002).

Neurological effects were observed after acute-duration exposure to ethylbenzene at concentrations equal to or higher than those that elicited auditory effects in animals. Effects observed after acute-duration exposure to ethylbenzene include moderate activation of motor behavior in rats exposed to 400 ppm (Molnar et al. 1986) and reduced activity and prostration and shallow breathing in rats and mice at 1,200 ppm (Ethylbenzene Producers Association 1986a). Rats or mice exposed to ≥2,000 ppm showed posture changes, reduced grip strength, reduced motor coordination (Tegeris and Balster 1994), narcotic effects (Molnar et al. 1986), and neurotransmission disturbances in the forebrain and hypothalamus (Andersson et al. 1981). Mice exposed to 4,060 ppm for 20 minutes showed a 50% reduction in respiratory rate (Nielsen and Alarie 1982). A 50% respiratory depression observed in mice at 1,432 ppm was attributed to sensory irritation (De Ceaurriz et al. 1981).

Increased liver weight was reported after acute-duration exposure in rats exposed to ≥400 ppm ethylbenzene (Ethylbenzene Producers Association 1986a; Toftgard and Nilsen 1982), but not in mice at 1,200 ppm or rabbits at 2,400 ppm (Ethylbenzene Producers Association 1986a). At these same levels and exposure durations, induction of microsomal enzymes and related ultrastructural changes (e.g., proliferation of the smooth endoplasmic reticulum) were observed. These effects occurred in the absence of histopathological changes to the liver. Therefore, the effects on the liver appear to be related to induction of microsomal enzymes in smooth endoplasmic reticulum. An increase in relative kidney weight was also observed in rats exposed to ≥1,200 ppm (Ethylbenzene Producers Association 1986a; Toftgard and Nilsen 1982), but not in mice at 1,200 ppm or rabbits at 2,400 ppm (Ethylbenzene Producers Association 1986a). However, increased kidney weights occurred in the absence of histological changes (Ethylbenzene Producers Association 1986a). No histopathological alterations were observed in the lungs of surviving rats, mice, or rabbits exposed to 1,200, 400, or 2,400 ppm ethylbenzene, respectively, for 4 days (Ethylbenzene Producers Association 1986a).

The observed damage to the auditory capacity of rats exposed to ethylbenzene during acute-duration studies reported in Cappaert et al. study (2000) was chosen as a critical effect to derive the acute-duration inhalation MRL. In the study by Cappaert et al. (2000), Wag/Rij rats (8 rats/group; sex not provided)

were exposed to 0, 300, 400, or 550 ppm ethylbenzene (99% pure) 8 hours/day for 5 days. Potential auditory effects were examined by measuring distortion product otoacoustic emissions (DPOAE), compound action potential (CAP), and hair cell counts at five locations of the organ of Corti 3–6 weeks after the last ethylbenzene exposure. Exposed animals did not show clinical signs of intoxication and there were no significant differences in terminal body weight between exposed and control rats. DPOAE amplitude growth curves showed a significant reduction in rats exposed to 550 ppm, but not to 300 or 400 ppm ethylbenzene. Effects were significant at 5.6, 8, and 11.3 kHz, but not at other frequencies. The DPOAE thresholds were significantly shifted (increased stimulus was needed to elicit the threshold response) at 5.6, 8, 11.3, and 16 kHz in rats in the 550-ppm group. DPOAE threshold shifts were not observed in other exposure groups. Animals exposed to 550 ppm showed a significant shift in the CAP amplitude growth curves at 8, 12, and 16 kHz. In the 400-ppm group, the CAP growth curves were affected only at 12 kHz and there was no effect in animals in the 300-ppm group. CAP thresholds were significantly shifted at 8, 12, and 16 kHz in the 550-ppm group and at 12 and 16 kHz in the 400-ppm group. There was no significant deterioration of CAP thresholds in the 300-ppm group. Significant OHC losses of approximately 33 and 75% were observed in the 550-ppm group in the auditory regions corresponding to 11 and 21 kHz, respectively. In the 400-ppm group, significant losses (25%) were observed in the 11 kHz region. OHC losses in the 21 kHz region in the 300-ppm group were approximately 12%, but were not statistically significantly different from controls. This study identifies a NOAEL of 300 ppm and a LOAEL of 400 ppm for significant deterioration in CAP auditory thresholds and significant OHC losses.

The point of departure for an acute-duration inhalation MRL was identified using benchmark dose (BMD) analysis of the CAP auditory threshold data using data from this study provided by Dr. Cappaert to ATSDR. The largest effects on CAP threshold occurred in response to 8, 12, and 16 kHz stimuli and, on this basis, these data were selected for BMD modeling. The BMD modeling was run using an internal dose metric (time-averaged arterial blood concentration of ethylbenzene, MCA), which was simulated using a physiologically-based pharmacokinetic (PBPK) model. Using MCA as the dose metric, the CAP threshold shift data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.1.1) using a benchmark dose response (BMR) of 1 standard deviation. Details of the BMD modeling and PBPK models are present in detail in Appendix A. At the 8 kHz frequency, the Hill, polynomial (2- and 3-degree), and power models provided adequate fit to the data. Of these models, the polynomial (3-degree) model provided the best fit to the data. At 12 and 16 kHz frequencies, only the Hill model provided an adequate fit to the data. The 95% lower confidence limit on the benchmark concentration ($BMDL_{MCA}$) for these three models are presented in Table 2-1.

Table 2-1. Human Equivalent Concentrations (HECs) for CAP Threshold Shifts

Effect	Model	$BMCL_{MCA}$ (µmol/L)	HEC[a] (ppm)
CAP threshold shift at 8 kHz	Polynomial (3-degree)	102.63	178.52
CAP threshold shift at 12 kHz	Hill	89.47	163.80
CAP threshold shift at 16 kHz	Hill	81.10	154.26

[a]Calculated using a reference human body weight of 70 kg and the assumption of 14-day continuous exposure.

$BMCL_{MCA}$ = 95% lower confidence limit on the benchmark concentration associated with a benchmark response of 1 standard deviation estimated using an MCA (time-weighted arterial blood concentration of ethylbenzene) dose metric; CAP = compound action potential

To select the point of departure for the acute-duration inhalation MRL, human equivalent concentrations (HECs) were predicted from the $BMCL_{MCA}$ values in Table 2-1 for CAP threshold data at 8, 12, and 16 kHz using the human PBPK model (estimation of the HEC values is described in Appendix A). The lowest HEC of 154.26 ppm was selected as the point of departure. This HEC was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) resulting in an acute-duration inhalation MRL of 5 ppm.

- An MRL of 2 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to ethylbenzene.

Several studies in animals, but no studies in humans, have examined the toxicity of ethylbenzene following intermediate-duration inhalation exposure. The available animal studies suggest that ototoxicity is the most sensitive end point of ethylbenzene toxicity. Rats exposed to ≥400 ppm ethylbenzene via inhalation for 4 or 13 weeks showed significant increases in auditory thresholds. These threshold shifts persisted unchanged for the duration of the exposure period and during an 8-week post-exposure recovery period (Gagnaire et al. 2007). Cell counts conducted in the organ of Corti after the 8-week recovery period showed significant losses of outer hair cells in rats exposed to ≥200 ppm. Concentration-related losses of inner hair cells (IHC) (14 and 32%) were observed in animals in the 600 and 800 ppm groups, respectively, with occasional IHC losses in the 400 ppm group.

Systemic effects have been observed at concentrations equal to or higher than those that elicited ototoxic effects in rats. Increased liver, kidney, lung, and spleen weights have been observed in animals exposed to ethylbenzene concentrations in the 250–1,000 ppm range (Cragg et al. 1989; Elovaara et al. 1985; NIOSH 1981; NTP 1992; Wolf et al. 1956). However, the changes in organ weight have not been associated with histological alterations. One study (Cragg et al. 1989) reported a small, but statistically significant, increase in platelet counts in male rats and leukocyte counts in female rats exposed to 782 ppm ethylbenzene for 4 weeks. Developmental effects have been observed in rats exposed to ≥1,000 ppm. Increases in the occurrence of skeletal malformations (NIOSH 1981; Saillenfait et al. 2003) and decreases in fetal body weight (Saillenfait et al. 2003, 2006, 2007) have been observed at ≥1,000 ppm. The NOAEL for these effects is 500 ppm (NIOSH 1981; Saillenfait et al. 2003, 2006, 2007). Developmental landmarks and neurodevelopment were not statistically or biologically significantly affected in the offspring of rats exposed to up to 500 ppm ethylbenzene in a two-generation reproductive toxicity study (Faber et al. 2006, 2007).

Thus, the available intermediate-duration inhalation studies suggest that ototoxicity is the most sensitive effect of ethylbenzene. Ototoxicity observed in the study by Gagnaire et al. (2007) was selected as the critical effect to derive the intermediate-duration inhalation MRL. In the Gagnaire et al. (2007) study, male Sprague-Dawley rats (14 rats/exposure group) were exposed to 0, 200, 400, 600, and 800 ppm ethylbenzene (99% pure) 6 hours/day, 6 days/week for 13 weeks. Ototoxicity was assessed based on effects on neurophysiological measurements after 4, 8, or 13 weeks of exposure and after a 8-week recovery period and cochlear total hair cell counts were measured at the end of the 8-week recovery period. There were no significant differences in body weight gain between the surviving treated animals and controls. Audiometric thresholds at 2, 4, 8, and 16 kHz were significantly higher in animals exposed to 400, 600, and 800 ppm ethylbenzene than in controls. The effect was evident at week 4, did not change throughout the exposure period, and was not reversed after 8 weeks of recovery. No shift in audiometric thresholds was observed in rats in the 200 ppm group; however, the morphological assessment of the organ of Corti showed significant losses (up to 30% of the outer hair cells in the mid frequency region) in the third row of the OHC in four of eight rats exposed to 200 ppm. A concentration-related loss in third row OHC (OHC3) was evident with almost complete loss observed in the 600 and 800 ppm groups. The data suggest that the extent of the damage at each concentration was greatest in the OHC3 followed, in decreasing order, by damage in OHC2, OHC1, and IHC. There was no significant hair cell loss in the control animals.

Auditory threshold shifts and OHC loss are selected as the critical effects following intermediate-duration inhalation exposure to ethylbenzene. BMD analysis was conducted for these end points using a data set provided to ATSDR by Dr. Gagnaire. The data for auditory thresholds at 4, 8, and 16 kHz in rats exposed for 4 or 13 weeks and OHC loss at the end of the recovery period were fit to all available continuous models in EPA's BMDS (version 2.1.1) using a time-averaged arterial blood concentration of ethylbenzene (MCA) as the dose metric and a BMR of 1 standard deviation change from control. The BMD modeling and the PBPK model used to estimate the MCA dose metric are described in Appendix A.

Most of the available BMD models did not adequately fit the auditory threshold data; however, with the exception of the auditory thresholds at 16 kHz in rats exposed to ethylbenzene for 13 weeks, one BMD model fit each data set often when the highest two dose groups were dropped. The $BMCL_{MCA}$ values estimated from these models are presented in Table 2-2. None of the BMD models adequately fit the OHC loss data. HECs corresponding to specific $BMCL_{MCA}$ values were simulated using a human PBPK model (described in Appendix A). The HECs of the $BMCL_{MCA}$ values (Table 2-2) ranged from 63.64 to

Table 2-2. Human Equivalent Concentrations (HECs) for Auditory Effects in Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 or 13 Weeks

Effect	Model	$BMCL_{MCA}$ µmol/L)	HEC[a] (ppm)
Auditory thresholds at 4 kHz following 4 weeks of exposure	Power (two highest doses dropped); nonconstant variance	33.12	87.13
Auditory thresholds at 8 kHz following 4 weeks of exposure	2-Degree polynomial (two highest doses dropped); nonconstant variance	19.94	63.64
Auditory thresholds at 16 kHz following 4 weeks of exposure	Power (two highest doses dropped); nonconstant variance	27.31	77.77
Auditory thresholds at 4 kHz following 13 weeks of exposure	Hill (all doses); nonconstant variance	28.59	79.95
Auditory thresholds at 8 kHz following 13 weeks of exposure	Power (two highest doses dropped); nonconstant variance	29.71	81.79

[a]Calculated using a reference human body weight of 70 kg and the assumption of 364-day continuous exposure.

$BMCL_{MCA}$ = 95% lower confidence limit on the benchmark concentration associated with a benchmark response of 1 standard deviation estimated using an MCA (time-weighted arterial blood concentration of ethylbenzene) dose metric

87.13 ppm; the lowest HEC of 63.64 ppm was selected as the point of departure for the MRL. This HEC was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) resulting in an intermediate-duration inhalation MRL of 2 ppm.

- An MRL of 0.06 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to ethylbenzene.

The chronic toxicity of inhaled ethylbenzene has been examined humans and in 2-year bioassays in rats and mice (NTP 1999). Hematological effects (increased average number of lymphocytes and decreased hemoglobin) were observed in workers exposed to solvents containing ethylbenzene (Angerer and Wulf 1985). In rats, concentration-related increases in the severity of nephropathy were observed in female rats exposed to ≥75 ppm and in male rats exposed to 750 ppm (NTP 1999). Increases in the incidence of renal tubule hyperplasia were also observed in male and female rats exposed to 750 ppm. The lowest LOAEL identified in mice was 250 ppm for hyperplasia of pituitary gland pars distalis observed in females; at 750 ppm, thyroid follicular cell hyperplasia was observed in male and female mice and hypertrophy and necrosis of the liver were observed in male mice (NTP 1999). These studies identify the kidney as a sensitive target following chronic-duration inhalation exposure to ethylbenzene and the NTP (1999) rat study was selected as the basis of the MRL.

In the NTP (1999) study, groups of male and female F344/N rats (50 animals/sex/dose group) were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation 6 hours/day, 5 days/week, for 104 weeks. Animals were observed twice daily and clinical findings were recorded monthly. Body weights were measured throughout the study and a complete necropsy and microscopic examination of major tissues and organs were performed on all rats. Survival of male rats in the 750 ppm group was significantly less than that of the chamber controls. No clinical findings were attributed to ethylbenzene exposure. Although the incidence of nephropathy (47/50, 43/50, 47/50, and 48/50 in males and 38/50, 42/50, 43/50, 46/49 in females) was not significantly different between the groups, significant increases in the severity of the nephropathy were observed in females at ≥75 ppm and in males at 750 ppm. The nephropathy severity scores in the 0, 75, 250, and 750 ppm groups were 2.3, 2.4, 2.3, and 3.5 in males, respectively, and 1.3, 1.6, 1.7, and 2.3 in females, respectively. Additionally, a significant increase in the incidence of renal tubule hyperplasia was observed in male rats exposed to 750 ppm. The incidences of renal tubule adenoma and adenoma or carcinoma (combined) in the 750-ppm group were significantly greater than the incidence in control animals. An increase in the incidence of cystic degeneration of the liver was also observed in male rats at 750 ppm.

Increased severity of chronic progressive nephropathy observed in female rats exposed to ≥75 ppm (NTP 1999) was selected as the critical effect for the MRL. BMD analysis was considered for determining the point of departure for the MRL; however, none of the available continuous exposure BMD models fit the data (standard errors calculated using the raw severity score data). Thus, a NOAEL/LOAEL approach was selected for calculating the point of departure; application of BMD analysis was precluded because standard errors or standard deviations were not provided for the nephropathy severity ratings. A PBPK model was developed (see Appendix A for details) to simulate two internal dose metrics for kidney effects: time-averaged arterial blood concentration of ethylbenzene (MCA) and time-averaged rate of metabolism of ethylbenzene expressed per kg body mass (MRAMKB). Both metrics were explored because current knowledge of the mechanisms of toxicity of ethylbenzene does not include an understanding of the relative contribution of parent compound or metabolites as proximate toxic agents in kidney. The internal dose metrics (MCA and MRAMKB) for each exposure level are presented in Table 2-3.

Human equivalent concentrations (HECs) corresponding to $LOAEL_{MCA}$ and $LOAEL_{MRAMKB}$ in female rats was estimated using a human PBPK model (described in Appendix A). The HECs were 17.45 ppm for the MCA dose metric and 52.68 ppm for the MRAMKB dose metric. Because there is limited information to determine whether the observed renal toxicity in female rats exposed to ethylbenzene is due to ethylbenzene or its metabolites, the lowest HEC value (17.45 ppm) was selected as the point of departure for the MRL. The HEC_{MCA} of 17.45 ppm was divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability) resulting in a chronic-duration inhalation MRL of 0.06 ppm.

Oral MRLs

No studies describing acute-duration oral exposure of humans to ethylbenzene were found in the literature. Two animal studies have examined the acute oral toxicity of ethylbenzene. An almost complete loss of the three rows of OHCs in the organ of Corti were reported in male rats administered 900 mg/kg/day (the only dose tested) by gavage for 2 weeks (Gagnaire and Langlais 2005). These losses were observed 10 days after the last dose. Although losses of OHCs have also been observed in acute-duration inhalation studies (Cappaert et al. 1999, 2000, 2001, 2002), Gagnaire and Langlais (2005) did not have a control group to establish the magnitude of the effects relative to unexposed animals; the study was used to rank the ototoxicity of 21 solvents administered by gavage. Nevertheless, the OHC losses observed in the ethylbenzene-treated animals were among the highest observed among the 21 organic

Table 2-3. Internal Dose Metrics for Male and Female F344/N Rats Exposed to Ethylbenzene 6 Hours/Day, 5 Days/Week for 104 Weeks

Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	MRAMKB (µmol/hour/kg body weight)
Male[a]		
0	0	0
75	4.12	8.92
250	27.66	23.64
750	146.77	43.05
Female[b]		
0	0	0
75	4.16	10.00
250	28.72	26.04
750	150.68	46.49

[a]Time weighted average body weight of 0.43 kg.
[b]Time weighted average body weight of 0.27 kg.

MCA = time-averaged arterial blood concentration; MRAMKB = time averaged rate of ethylbenzene metabolism expressed per kg body mass

solvents tested (Gagnaire and Langlais 2005). The 900 mg/kg/day dose was considered a serious LOAEL for ototoxicity. In the second study, doses of 500 or 1,000 mg/kg ethylbenzene decreased luteinizing hormone, progesterone, and 17 β-estradiol levels, increased stromal tissue with dense collagen bundles and reduced lumen in the uterus, and delayed the estrus cycle in female rats during the diestrus stage (Ungvary 1986). Interpretation of the results of this study is limited by the poor reporting of the study methods and results and the lack of statistical analysis. Because the only dose tested in the Gagnaire and Langlais (2005) study is a serious LOAEL, an acute-duration oral MRL cannot be derived for ethylbenzene.

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to ethylbenzene.

The intermediate-duration oral database for ethylbenzene is limited to a study conducted by Mellert et al. (2007) evaluating the effects of oral exposure of rats to ethylbenzene for 4 and 13 weeks, and a poorly reported 6-month exposure study in rats (Wolf et al. 1956). The 4- and 13-week studies by Mellert et al. (2007) found effects consistent with hepatotoxicity including increased absolute and relative liver weights, increased incidence of hepatocyte centrilobular hypertrophy, and increased serum liver enzyme activities in rats administered ≥250 mg/kg/day. Kidney effects, including increases in increases in relative kidney weight and hyaline droplet nephropathy were observed in males administered ≥250 mg/kg/day; however, these effects were most likely secondary to increases of α2μ-globulin accumulation, and, therefore, considered not relevant to humans. Wolf et al. (1956) also reported liver effects (characterized by cloudy swelling of parenchymal cells of the liver and an increase in liver weight) in female rats administered 408 mg/kg/day by gavage for 6 months. No other hepatic changes were reported. However, this study was poorly reported and did not provide adequate descriptions of study methods or results.

Based on evidence of hepatotoxicity (increased serum liver enzyme activity, absolute and relative liver weights, dose-related increased incidence of centrilobular hepatocyte hypertrophy), and the lack of evidence for adverse effects in other tissues or organ systems at lower oral intermediate-duration dosages, liver effects were selected as the basis for deriving the intermediate oral MRL. The principal study (Mellert et al. 2007) identified NOAEL and LOAEL values for hepatotoxicity of 75 and 250 mg/kg/day, respectively, in rats administered ethylbenzene for 13 weeks. In this study (Mellert et al. 2007), groups of 10 male and 10 female Wister rats were administered ethylbenzene (no vehicle) by gavage at doses of 0, 75, 250, or 750 mg/kg/day for 13 weeks. The total daily dose of ethylbenzene was administered as split morning/evening half doses. Animals were examined daily for mortality and clinical signs and food and

water consumption and body weights were recorded weekly. A detailed clinical examination (ophthalmology and a functional observational battery [FOB]) and assessment of motor activity were conducted during the last week of treatment. After 13 weeks, urinalysis was conducted and blood samples were obtained and analyzed for hematology and clinical chemistry; organ weights were recorded and gross histopathologic examinations of the liver, kidney, and pancreas were conducted on animals in all groups. A comprehensive histopathological examination of tissues was performed in the control and 750 mg/kg/day groups. No mortalities were observed during the course of the study. Clinical signs (post-dosing salivation) in treated animals were observed in all animals administered ≥250 mg/kg/day and in one animal administered 75 mg/kg/day. Terminal body weight in males was significantly decreased by 14% compared to controls in the 750 mg/kg/day group. Mean corpuscular volume was increased in males and females and platelet count was reduced in females treated with 750 mg/kg/day. Prothrombin time was significantly decreased (<8% compared to controls) in females administered ≥250 mg/kg/kg, but no changes in prothrombin times were observed in males in any treatment group. Effects indicative of liver toxicity (summarized in Table 2-4) included increased activity of serum liver enzymes (alanine aminotransferase and γ-glutamyl transferase), increased absolute and relative liver weights, and a dose-related increase in the incidence of centrilobular hepatocyte hypertrophy. Although some alterations in other serum chemistry parameters were found, the study investigators considered them to be due to adaptive effects in the liver.

Renal effects in males included increased serum creatinine (750 mg/kg/day), increased incidences of transitional epithelial cells and granular and epithelial cell casts in the urine (≥250 mg/kg/day), increased absolute and relative kidney weights (≥250 mg/kg/day), and a dose-related increase in severity of hyaline droplet nephropathy (≥250 mg/kg/day). Adverse renal effects in males were most likely related to accumulation of α2μ-globulin accumulation, and, therefore, considered not relevant to humans. Absolute kidney weight was significantly increased by 7 and 13% in females administered 250 and 750 mg/kg/day, respectively, compared to controls. However, since no histopathological findings or alterations in urinalysis parameters were observed, increased kidney weight in females was not considered adverse. Absolute and relative thymus weights were decreased in females treated with ≥250 mg/kg/day, but no histopathological findings were observed. Histopathological examination of all other tissues did not reveal any abnormalities. Results of the FOB did not reveal consistent treatment-related effects. NOAEL and LOAEL values of 250 and 750 mg/kg/day, respectively, were identified based on hepatotoxicity in male and female rats.

Table 2-4. Effects on Serum Liver Enzymes, Liver Weights, and Liver Histopathology in Male and Female Rats Exposed to Oral Ethylbenzene for 13 Weeks

	Dose group (mg/kg/day)			
Parameter	0	75	250	750
Males				
ALT(µkat/L)	0.62±0.12[a]	0.70±0.12	0.89±0.26[b]	1.11±0.23[b]
GGT (nkat/L)	2±3	6±6	10±6[b]	10±6[b]
Absolute liver weight (g)	8.02±0.55	8.26±0.81	10.25±0.98[b]	9.88±0.98[b]
Liver/body weight (%)	2.26±0.08	2.36±0.08[b]	3.01±0.14[b]	3.31±0.13[b]
Centrilobular hepatocyte hypertrophy (incidence)	1/10	1/10	6/10[c]	8/10[b]
Females				
ALT(µkat/L)	0.58±0.18	0.55±0.08	0.60±0.12	0.73±0.19[c]
Absolute liver weight (g)	5.40±0.30	5.72±0.53	6.11±0.36[b]	7.15±0.50[b]
Liver/body weight (%)	2.63±0.13	2.70±0.16	3.03±0.12[b]	3.52±0.18[b]
Centrilobular hepatocyte hypertrophy (incidence)	0/10	0/10	5/10[c]	10/10[b]

[a]values are mean±standard deviation.
[b]p≤0.01.
[c]p≤0.05.

ALT = alanine aminotransferase; GGT = γ-glutamyl transferase

Source: Mellert et al. 2007

Based on evidence of hepatotoxicity (increased serum liver enzyme activity, absolute and relative liver weights, and incidence of centrilobular hepatocyte hypertrophy), the liver was identified as the most sensitive target for oral ethylbenzene, with NOAEL and LOAEL values of 75 and 250 mg/kg/day, respectively. Since serum liver enzyme activities were increased in the 250 and 750 mg/kg/day groups in males, but only in the 750 mg/kg/day group in females, males appeared more sensitive than females to hepatic effects of oral ethylbenzene.

To determine the point of departure for derivation of the intermediate-duration MRL, data sets for serum liver enzymes (alanine aminotransferase and γ-glutamyl transferase), absolute liver weight, relative liver weight, and centrilobular hepatocyte hypertrophy in male rats were evaluated for suitability for BMD modeling using EPA's BMDS (version 2.1.1). A PBPK model was developed to simulate two internal dose metrics for liver effects: time-averaged concentration of ethylbenzene in liver (MCL) and time-averaged rate of metabolism of ethylbenzene in liver (MRAMKL). The assumption of using the MCL metric is that the liver response is correlated with the time-averaged concentration of ethylbenzene in liver. The assumption in using the MRAMKL metric is that the liver response is correlated with the time-averaged rate of production of ethylbenzene metabolites in liver. Both metrics were explored because current knowledge of the mechanism of toxicity of ethylbenzene does not include an understanding of the relative contributions of parent compound or metabolites as proximate toxic agents in liver. Detailed discussions of the BMD modeling and PBPK model are presented in Appendix A.

Using the MCL and MRAMKL dose metrics, data for alanine aminotransferase, γ-glutamyl transferase, absolute liver weight, and relative liver weight were analyzed using all available continuous variable BMD models and a BMR of 1 standard deviation change from control and incidence data for centrilobular hepatocyte hypertrophy were analyzed using all available dichotomous BMD models and the extra risk option with a BMR of 10% extra risk. The BMD analysis identified nine BMDL values that could be used as the point of departure for the intermediate-duration oral MRL; these values are presented in Tables 2-5 and 2-6. For each end point and dose metric, human equivalent doses (HEDs) were estimated from the BMDL value using the human PBPK model (discussed in Appendix A); the HEDs are summarized in Tables 2-5 and 2-6.

The lowest HEDs were calculated from the $BMDL_{MCL}$ and $BMDL_{MRAMKL}$ for centrilobular hepatocyte hypertrophy. Because there is limited information to determine whether the observed hepatic effects are due to ethylbenzene or its metabolites, the lowest HED value (10.68 mg/kg/day) was selected as the point of departure for the MRL. The HED was divided by an uncertainty factor of 30 (3 for extrapolation from

Table 2-5. Benchmark Doses and Human Equivalent Doses for Liver Effects Using Arterial Ethylbenzene Concentration (MCL) Dose Metric

Effect	Model	BMDL (µmol/L)	HED[a] (mg/kg/day)
Increased alanine aminotransferase	Hill (all doses); constant variance	7.49	11.82
Increased γ-glutamyl transferase	Inadequate fit to all models		
Increased absolute liver weights	Linear (highest dose dropped); constant variance	32.17	31.82
Increased relative liver weights	Linear (highest dose dropped); constant variance	13.53	18.47
Centrilobular hepatocyte hypertrophy	Log logistic	6.61	10.68

[a]Calculated using a reference human body weight of 70 kg and the assumption that the daily dose was delivered in 16 dose splits/24 hours (i.e., only exposed during waking hours).

BMDL = 95% lower confidence limit on the benchmark dose; HED = human equivalent dose; MCL = time-averaged concentration of ethylbenzene in liver

Table 2-6. Benchmark Doses (BMDs) and Human Equivalent Doses (HEDs) for Liver Effects Using MRAMKL Internal Dose Metric

Effect	Model[a]	BMDL (µmol/hour/kg liver)	HED[b] (mg/kg/day)
Increased alanine aminotransferase	3-Degree polynomial; nonconstant variance	391.02	31.06
Increased γ-glutamyl transferase	Linear; constant variance	737.62	111.37[c]
Increased absolute liver weights	Hill; constant variance	548.01	48.62
Increased relative liver weights	2-Degree polynomial; constant variance	390.47	31.01
Centrilobular hepatocyte hypertrophy	Multistage (3-degree polynomial)	206.91	15.48

[a]All doses used for BMD modeling.
[b]Calculated using a reference human body weight of 70 kg and the assumption that the daily dose was delivered in 16 dose splits/24 hours (i.e., only exposed during waking hours).
[c]Approximate value, value is very close to the metabolism Vmax.

BMDL = 95% lower confidence limit on the benchmark dose; MRAMKL = time-averaged rate of metabolism of ethylbenzene in liver

animals to humans using dosimetric adjustments and 10 for human variability), resulting in an intermediate-duration oral MRL of 0.4 mg/kg/day.

No studies describing the non-carcinogenic effects of chronic-duration oral exposure to ethylbenzene in humans were located. Available chronic-duration oral exposure studies in animals (Maltoni et al. 1985, 1997) did not evaluate comprehensive noncancer end points and, therefore, do not provide suitable data for derivation of a chronic-duration oral MRL.

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located regarding lethality in humans following inhalation exposure to ethylbenzene. Matsumoto et al. (1992) reported the case of a 44-year-old man who died 9 days after exposure to gasoline vapors for at least 10 hours in an enclosed car. The patient’s clothing was saturated with gasoline, but there was no apparent ingestion of gasoline. The patient suffered chemical burns over 50% of the total body surface area, and the cause of death was reported as multiple organ failure. Ethylbenzene was detected in the patient’s blood (estimated initial blood concentration of 2.6 µg/mL). However, since gasoline contains approximately 1.4% (by weight) ethylbenzene (Agency for Toxic Substances and Disease Registry 1995), it is unlikely that death was due to ethylbenzene exposure.

Studies on the lethality of inhaled ethylbenzene have been conducted using several animal models, with exposure times ranging from a few hours to 2 years. The LC_{50} values obtained from acute inhalation exposure studies were 13,367 ppm following a 2-hour exposure (Ivanov 1962) and 4,000 ppm following a 4-hour exposure (Smyth et al. 1962); 100% mortality was observed following exposure to 16,698 ppm for 2 hours (Ivanov 1962) and exposure to 8,000 ppm for 4 hours (Smyth et al. 1962). Inhalation exposure of Fischer 344 rats and $B6C3F_1$ mice to ethylbenzene for 6 hours/day for 4 days produced lethality at concentrations of 1,200 and 2,400 ppm, respectively, although exposure to concentrations up to 2,400 ppm was not lethal to rabbits (Ethylbenzene Producers Association 1986a). In intermediate-duration exposure studies, inhalation exposure of rats and mice to 782 ppm or rabbits to 1,610 ppm

ethylbenzene for 4 weeks did not produce lethality (Cragg et al. 1989). No mortality was observed in rats or mice exposed to 782 ppm or rabbits exposed to 1,610 ppm ethylbenzene for 4 weeks (Cragg et al. 1989) or in rats or mice exposed to 975 ppm ethylbenzene for 90 days (NTP 1992). Survival of male rats, but not female rats or male or female mice, exposed to 750 ppm ethylbenzene for 2 years was significantly decreased (NTP 1999); survival in male rats exposed to 75 or 250 ppm ethylbenzene was not affected.

The LC_{50} values and all reliable LOAEL values for death in rats and mice following acute- or chronic-duration exposure are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

Little data are available on the systemic effects of inhaled ethylbenzene in humans. Most of the information available is from case reports in which quantitative data on exposure concentrations and durations were not reported. In addition, most of the available studies have confounding factors (e.g., simultaneous exposures to other toxic substances) and insufficient reporting of important study details. In general, the systemic effects observed in humans were respiratory tract and ocular irritation, and possible ototoxicity (hearing loss) and hematological alterations (increased lymphocyte counts and decreased hemoglobin concentration) (Angerer and Wulf 1985; Cometto-Muñiz and Cain 1995; Thienes and Haley 1972; Yant et al. 1930).

Several studies were located on the systemic effects of ethylbenzene in animals following inhalation exposure. Acute- and intermediate-duration exposure to inhaled ethylbenzene is associated with respiratory irritation, changes to the liver (increased organ weights and induction of microsomal enzymes), and effects on the hematological system (decreased platelets and increased leukocyte counts). Chronic exposure is associated with adverse effects to the liver (necrosis and hypertrophy), kidney (nephropathy and hyperplasia), and endocrine system (thyroid and pituitary hyperplasia).

No studies were located describing cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, dermal, body weight, or metabolic effects in humans, or dermal effects in animals after inhalation exposure to ethylbenzene.

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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 (Fischer- 344)	4 d 6 hr/d				2400 M (100% mortality by day 3)	Ethylbenzene Producers Association 1986a	
2	Rat (NS)	4 hr				4000 M (LC50)	Smyth et al. 1962	
3	Mouse (B6C3F1)	4 d 6 hr/d				1200 M (4/5 animals died by day 3)	Ethylbenzene Producers Association 1986a	
Systemic								
4	Rat (Wistar)	2 wk 5 d/wk 6 hr/d	Hepatic		50 M (induction of UDP-glucuronyl transferase and D-glucuronyllactone dehydrogenase)		Elovaara et al. 1985	
			Renal		600 M (increase in relative kidney weights)			

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
5	Rat (Fischer- 344)	4 d 6 hr/d	Resp	2000 M			Ethylbenzene Producers Association 1986a	No liver or renal histopathological changes were observed.
			Hepatic		400 M	(increased liver weight)		
			Renal	400 M	1200 M	(increased relative kidney weight)		
			Ocular	400 M	1200 M	(lacrimation)		
			Bd Wt	1200 M				
6	Rat (Sprague-Dawley)	3 d 6 hr/d	Resp	2000 M			Toftgard and Nilsen 1982	
			Hepatic		2000 M	(increased relative liver weight, and induction of nadph-cytochrome reductase and 7-ethoxycoumarin o-deethylase)		
			Renal		2000 M	(increased relative kidney weight)		
7	Mouse (Swiss)	5 min	Resp		1432 M	(RD50)	De Ceaurriz et al. 1981	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
8	Mouse (B6C3F1)	4 d 6 hr/d	Ocular		400 M (lacrimation)		Ethylbenzene Producers Association 1986a	
			Bd Wt	400 M				
9	Mouse (Swiss-Webster)	30 min	Resp		4060 M (RD50)		Nielsen and Alarie 1982	
10	Mouse (CFW)	20 min	Ocular		2000 M (lacrimation and palpebral closure)		Tegeris and Balster 1994	
11	Rabbit (New Zealand)	4 d 6 hr/d	Resp	2400 M			Ethylbenzene Producers Association 1986a	
			Hepatic	2400 M				
			Renal	2400 M				
			Ocular		400 M (lacrimation)			
			Bd Wt	2400 M				
Neurological								
12	Rat (Wag/Rij/Cpb/I	8 hr/d 5 d				800 M (loss of outer hair cells and hearing loss)	Cappaert et al. 1999	
13	Rat (Wag/Rij)	8 hr 5 d		300[b]		400 (loss of outer hair cells and shifts in hearing thresholds)	Cappaert et al. 2000	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
14	Rat (albino Wag/Rij)	8 hr/d 5 d		300	400 (loss of outer hair cells)		Cappaert et al. 2001	
15	Rat (Wag/Rij)	8 hr/d 5 d			550 F (loss of outer hair cells and shifts in hearing thresholds)		Cappaert et al. 2002	
16	Rat (Fischer- 344)	4 d 6 hr/d		1200 M		2400 M (salivation, prostration)	Ethylbenzene Producers Association 1986a	
17	Rat (CFY)	4 hr		200 M	400 M (moderate activation in motor behavior)	2180 M (narcotic effects)	Molnar et al. 1986	
18	Mouse (B6C3F1)	4 d 6 hr/d		400 M		1200 M (prostration and reduced activity)	Ethylbenzene Producers Association 1986a	
19	Mouse (CFW)	20 min			2000 M (postural changes, decreased arousal and rearing, distrubed gait, decreased mobility, righting reflex, decreased grip strength, increased landing foot splay, impaired psychomotor coordination)		Tegeris and Balster 1994	

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
20	Rabbit (New Zealand)	4 d 6 hr/d		2400 M			Ethylbenzene Producers Association 1986a	
Reproductive								
21	Rat (Fischer- 344)	4 d 6 hr/d		2400 M			Ethylbenzene Producers Association 1986a	
22	Mouse (B6C3F1)	4 d 6 hr/d		1200 M			Ethylbenzene Producers Association 1986a	
23	Rabbit (New Zealand)	4 d 6 hr/d		2400 M			Ethylbenzene Producers Association 1986a	

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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								
24	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d	Resp	782			Cragg et al. 1989	
			Cardio	782				
			Gastro	782				
			Hemato	382	782	(increased platelet counts in males; increased mean total leukocyte counts in males and females)		
			Musc/skel	782				
			Hepatic	382	782	(increased absolute and relative liver weight)		
			Renal	782				
			Endocr	782				
			Ocular	99	382	(sporadic incidence of lacrimation)		
			Bd Wt	782				

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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	Rat (Wistar)	5-16 wk 5 d/wk 6 hr/d	Hepatic		50 M (induction of UDP-glucuronyl transferase and D-glucuronyllactone dehydrogenase)		Elovaara et al. 1985	
			Renal		300 M (increase in microsomal enzyme activity and glutathione)			
			Bd Wt	600 M				
26	Rat (Wistar)	3 wk 5 d/wk 7 hr/d Gd 1-19	Resp	985 F			NIOSH 1981	
			Hepatic	97 F	959 F (increased liver weight)			
			Renal	97 F	959 F (increased kidney weight)			
			Bd Wt	985 F				

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
27	Rat (F344/N)	90 d 5 d/wk 6 hr/d	Resp	99 F	246 F (increased absolute and relative lung weight)		NTP 1992	
			Cardio	975				
			Gastro	975				
			Hemato	975				
			Musc/skel	975				
			Hepatic	99 M	246 M (increased absolute and relative liver weight)			
			Renal	246 M	498 M (<10% increase in absolute and relative kidney weight)			
			Endocr	975				
			Ocular	975				
			Bd Wt	975				
28	Rat SD	6 hr/d Gd 6-20	Hepatic		250 F (increased absolute and relative liver weight, moderate to marked hepatocellular hypertrophy)		Saillenfait et al. 2006, 2007	
			Bd Wt	250 F	1000 F			

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
29	Rat (CD)	6 hr/d 7 d/wk	Hemato	500 F			Stump 2004	
			Bd Wt	500 F				
30	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d	Resp	782			Cragg et al. 1989	
			Cardio	782				
			Gastro	782				
			Hemato	782				
			Musc/skel	782				
			Hepatic	382	782 (increased absolute and relative liver weight)			
			Renal	782				
			Endocr	782				
			Ocular	782				
			Bd Wt	782				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
31	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d	Resp	975			NTP 1992	
			Cardio	975				
			Gastro	975				
			Hemato	975				
			Musc/skel	975				
			Hepatic	498 M	740 M (increased absolute and relative liver weight)			
			Renal	740 F	975 F (increased relative kidney weight)			
			Endocr	975				
			Ocular	975				
			Bd Wt	975				

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
32	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d	Resp	1610			Cragg et al. 1989	
			Cardio	1610				
			Gastro	1610				
			Hemato	1610				
			Musc/skel	1610				
			Hepatic	1610				
			Renal	1610				
			Endocr	1610				
			Ocular	1610				
			Bd Wt	1610				
33	Rabbit (New Zealand)	Gd 1-24 7 d/wk 7 hr/d	Resp	962 F			NIOSH 1981	
			Hepatic	99 F	962 F	(increased absolute and relative liver weights in pregnant rabbits)		
			Renal	962 F				
			Bd Wt	962 F				
			Other	962 F				
Immuno/ Lymphoret								
34	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989	

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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)	3 wk 5 d/wk 7 hr/d Gd 1-19		97 F	959 F (increased spleen weight)		NIOSH 1981	
36	Rat (F344/N)	90 d 5 d/wk 6 hr/d		975			NTP 1992	NOAEL based on evaluation of thymus weight, gross pathology, histopathology, and hematology.
37	Rat (CD)	6 hr/d 7 d/wk		500 F			Stump 2004	Based on absence of splenic IgM antibody forming response to immunization with T cell-dependent antigen (sheep RBC)
38	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989	NOAEL based on evaluation of thymus and spleen weight, gross pathology, histopathology, and hematology.
39	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		975			NTP 1992	NOAEL based on evaluation of thymus weight, gross pathology, histopathology, and hematology.

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d		1610			Cragg et al. 1989	
Neurological								
41	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d		99	382 (sporadic incidence of salivation)		Cragg et al. 1989	
42	Rat (SD)	6 hr/d 6 d/wk 13 wk			200[c] M	600 M (complete loss of third row outer hair cells and hearing loss)	Gagnaire et al. 2007	
43	Rat (F344/N)	90 d 5 d/wk 6 hr/d		975			NTP 1992	
44	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989	NOAEL based on clinical observations, organ weights, and histopathology.
45	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		975			NTP 1992	NOAEL based on clinical observations, organ weights, and histopathology.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
46	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d		1610			Cragg et al. 1989	NOAEL based on clinical observations, organ weights, and histopathology.
Reproductive								
47	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989	NOAEL based on histopathological examination of reproductive organs.
48	Rat (Crl-CD)	6 hr/d 70 d		500			Faber et al. 2006	NOAEL based on reproductive parameters (mating/fertility indices, gestation length, implantations, births/litter and litter size.
49	Rat (Wistar)	3 wk 5 d/wk 7 hr/d Gd 1-19		985 F			NIOSH 1981	NOAEL assessed by pregnancy rate, implantations, number of litters, resorptions, and live fetuses.
50	Rat (F344/N)	90 d 5 d/wk 6 hr/d		975			NTP 1992	NOAEL based on vaginal cytology and sperm motility, organ weights, and estrous cycle.

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
51	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989	NOAEL based on histopathological examination of reproductive organs.
52	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		975			NTP 1992	NOAEL based on vaginal cytology and sperm motility, organ weights, and estrous cycle.
53	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d		1610			Cragg et al. 1989	NOAEL based on histopathological assessment of reproductive organs.
54	Rabbit (New Zealand)	Gd 1-24 7 d/wk 7 hr/d		962 F			NIOSH 1981	NOAEL assessed by pregnancy rate, implantations, number of litters, resorptions, and live fetuses.
Developmental								
55	Rat (Crl-CD)	6 hr/d 70 d		500 F			Faber et al. 2006	NOAEL based on fetal survival and gross and histopathological examination of fetuses.

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
56	Rat (Crl-CD)	6 hr/d 70 d		500 F			Faber et al. 2007	NOEAL based on fetal survival, body weights, physical landmarks, and neurobehavioral tests.
57	Rat (Wistar)	3 wk 5 d/wk 7 hr/d Gd 1-19		97 F	959 F (extra rib, supemumerary ribs)		NIOSH 1981	
58	Rat (Sprague-Dawley)	6 hr/d Gd 6-20		500 F	1000 F (decreased fetal body weight)		Saillenfait et al. 2003	
59	Rat (Sprague-Dawley)	6 hr/d Gd 6-20		250 F	1000 F (slight decrease in fetal body weight)		Saillenfait et al. 2006, 2007	
60	Rabbit (New Zealand)	Gd 1-24 7 d/wk 7 hr/d		962 F			NIOSH 1981	NOAEL assessed by pregnancy rate, implantations, number of litters, resorptions, and live fetuses.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Death								
61	Rat (F344)	6 hr/d 5 d/wk 2 yr				750 M (decreased survival)	NTP 1999	Survival of male rats was not affected at 75 or 250 ppm. In addition, survival of female rats and male and female mice was not affected at 750 ppm.
Systemic								
62	Rat (F344)	6 hr/d 5 d/wk 2 yr	Resp	750			NTP 1999	
			Cardio	750				
			Hemato	750				
			Musc/skel	750				
			Hepatic	750				
			Renal		75[d] F (increased severity of nephropathy)			
			Endocr	750				
			Dermal	750				
			Bd Wt	750				

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
63	Mouse (F344)	6 hr/d 5 d/wk 2 yr	Resp	750			NTP 1999	
			Cardio	750				
			Gastro	750				
			Musc/skel	750				
			Hepatic	250 M	750 M (hypertrophy and necrosis)			
			Renal	750				
			Endocr	75 F	250 F (hyperplasia in pituitary gland pars distalis)			
					750 (thyroid follicular cell hyperplasia)			
			Dermal	750				
			Bd Wt	750				
Cancer								
64	Rat (F344)	6 hr/d 5 d/wk 2 yr				750 M (CEL: renal tubule adenoma or carcinoma)	NTP 1999	

Table 3-1 Levels of Significant Exposure to Ethylbenzene - 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
65	Mouse (F344)	6 hr/d 5 d/wk 2 yr				750	(CEL: alveolar/bronchiolar adenoma or carcinoma and hepatocellular adenoma or carcinoma)	NTP 1999	

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

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 5 ppm based on a BMCL using an internal dose metric to simulate time averaged arterial blood concentration of ethylbenzene (81.10 µmol/L); a human equivalent concentration (HEC) of the BMCL was estimated using a human PBPK model. The BMCL(HEC) (154.26 ppm) was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

c Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 2 ppm based on a BMCL using an internal dose metric to simulate time averaged arterial blood concentration of ethylbenzene (19.94 µmol/L); a human equivalent concentration (HEC) of the BMCL was estimated using a human PBPK model. The BMCL(HEC) (63.64 ppm) was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

d Used to derive a chronic-duration inhalation minimal risk level (MRL) of 0.06 ppm based on an internal dose metric (averaged arterial blood concentration of ethylbenzene, MCA) of the LOAEL; a human equivalent concentration (HEC) of the LOAEL(MCA) was estimated using a human PBPK model. The LOAEL(HEC) (17.45 ppm) was divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestation day(s); Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; RD50 = exposure concentration producing a 50% decrease in respiratory rate ; Resp = respiratory; wk = week(s); yr = year(s)

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

Acute (≤14 days)

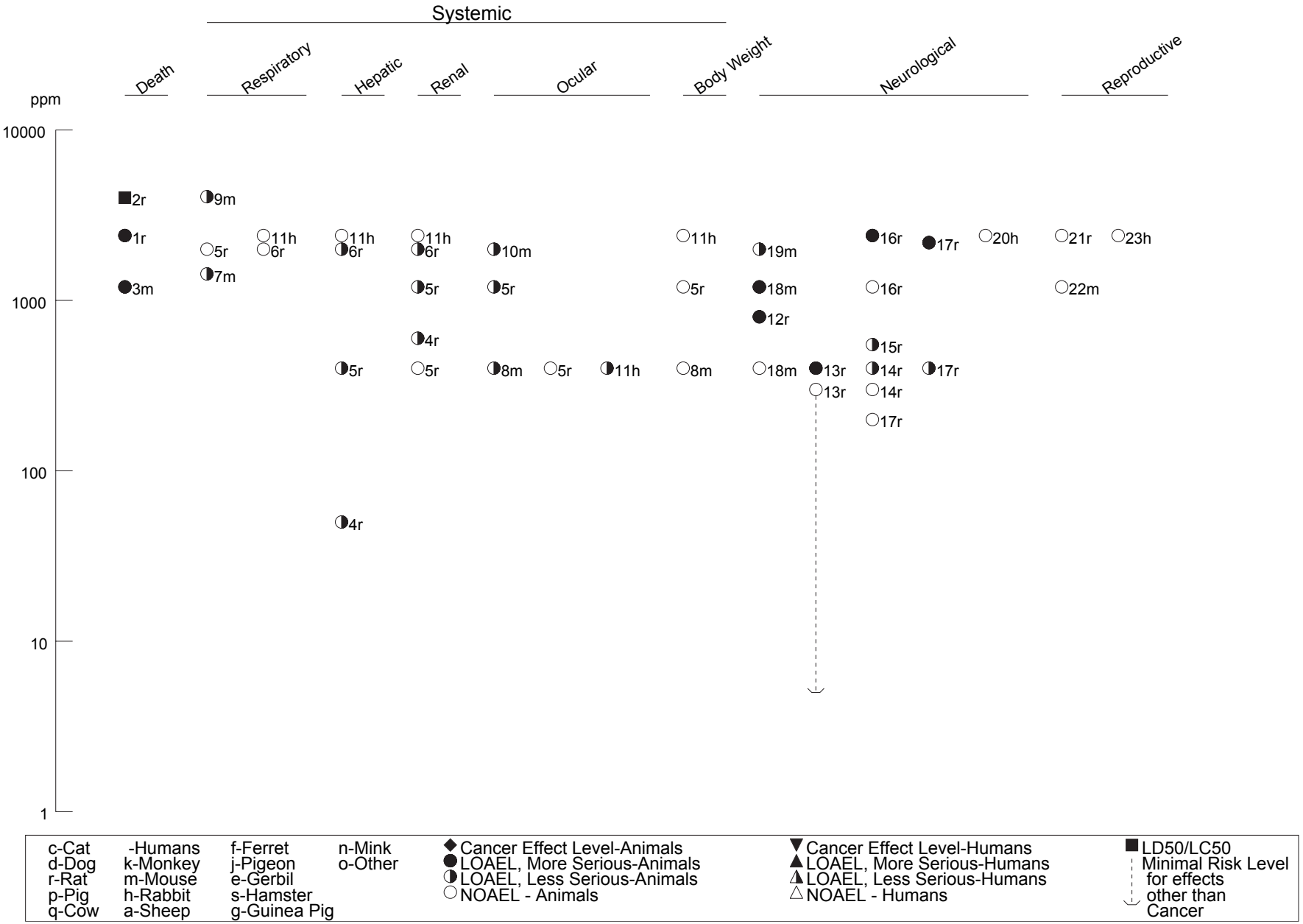


Figure 3-1 Levels of Significant Exposure to Ethylbenzene - Inhalation *(Continued)*

Intermediate (15-364 days)

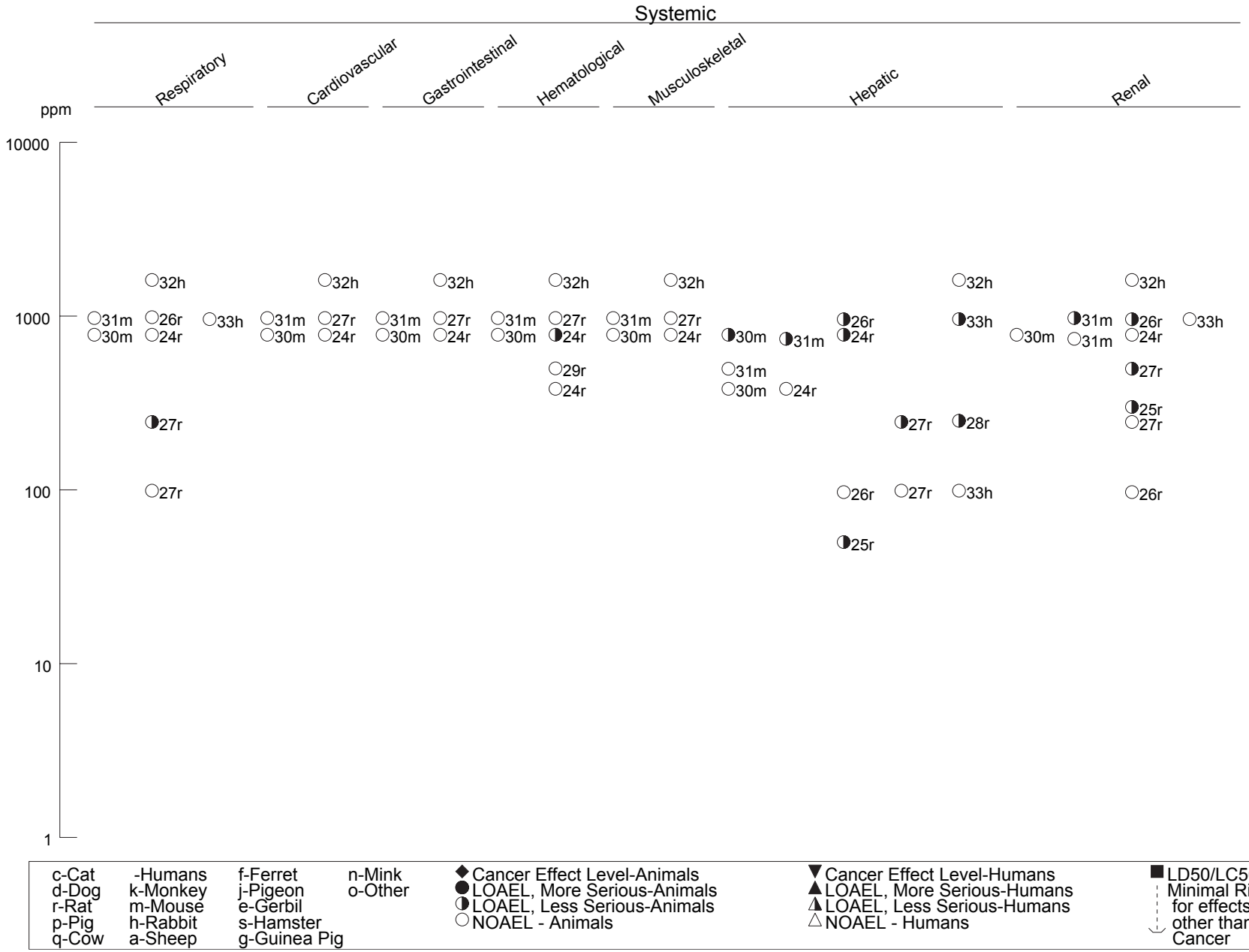


Figure 3-1 Levels of Significant Exposure to Ethylbenzene - Inhalation *(Continued)*

Intermediate (15-364 days)

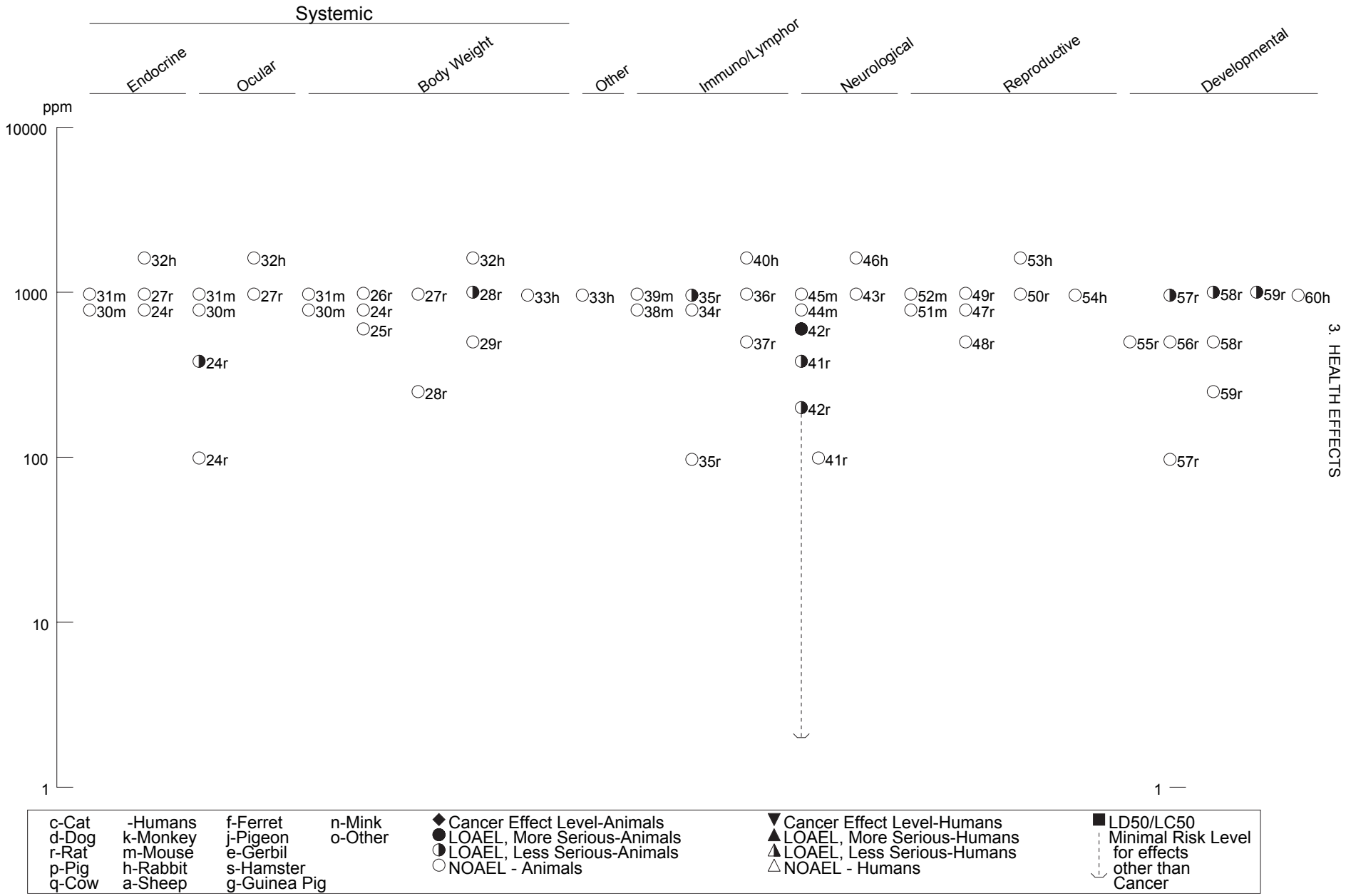
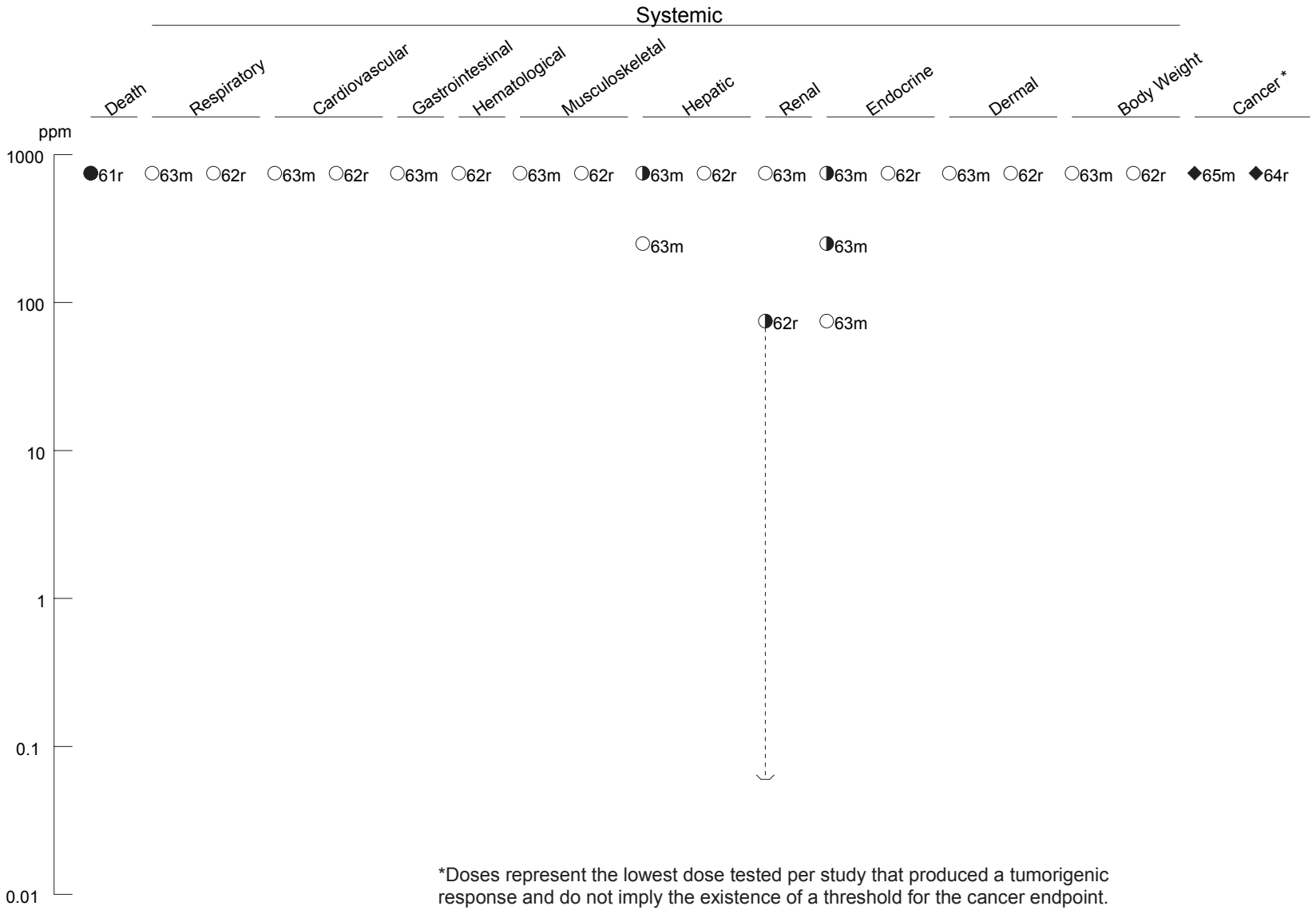


Figure 3-1 Levels of Significant Exposure to Ethylbenzene - Inhalation *(Continued)*

Chronic (≥365 days)



The systemic effects observed after inhalation exposure are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Male volunteers reported throat and nasal irritation and feelings of "chest constriction" during a 6-minute inhalation exposure to 2,000 ppm ethylbenzene (Yant et al. 1930). More severe throat and nasal irritation were reported immediately upon exposure to 5,000 ppm ethylbenzene. No data on pulmonary function were reported (Yant et al. 1930). No bronchospastic response was observed in two subjects challenged with 55 ppm ethylbenzene for 15 minutes in an inhalation chamber, based on comparison of pre- and post-exposure pulmonary function tests (Moscato et al. 1987).

Results of acute studies in animals indicate that inhalation of ethylbenzene produces adverse respiratory effects ranging from irritation to pulmonary congestion. Nasal irritation (based on nose rubbing) was observed in guinea pigs exposed to 1,000 ppm for 3 and 8 minutes and to 2,000, 5,000, and 10,000 ppm for 480, 30, and 10 minutes, respectively (Yant et al. 1930). Gross histopathology revealed congestion and edema in the lungs of animals that died after exposure to 10,000 ppm ethylbenzene, with less severe effects observed in surviving animals. Pulmonary congestion also was observed in rats and mice that died during exposure a 4-day exposure to 2,400 and ≥1,200 ppm ethylbenzene, respectively (Ethylbenzene Producers Association 1986a). A 50% reduction in breathing rate was observed in mice exposed to 1,432 ppm for 5 minutes (De Ceaurriz et al. 1981) and 4,060 ppm for 30 minutes (Nielsen and Alarie 1982). No adverse respiratory effects were observed in rats exposed to 2,000 ppm for 3 days (Toftgard and Nilsen 1982) or in rats, mice, and rabbits exposed to 1,200, 400, or 2,400 ppm, respectively, for 4 days (Ethylbenzene Producers Association 1986a).

Adverse respiratory effects attributed to intermediate- or chronic-duration inhalation exposures to ethylbenzene have been observed in animals. Relative lung weight was increased in male rats exposed to 975 ppm for 90 days, although increased absolute and relative lung weights were observed only in female rats exposed to 246 ppm ethylbenzene, but not to higher concentrations (NTP 1992). Pulmonary lesions (inflammatory cell infiltrate) were observed in male rats exposed to ≥246 ppm for 90 days (NTP 1992). However, the NTP Pathology Working Group considered these effects to be more typical of an infectious agent than a response to the test compound; therefore, pulmonary findings were not attributed to ethylbenzene exposure. No histopathological changes were observed in rats exposed to 2,200 ppm, guinea pigs or rabbits exposed 1,250 ppm, or monkeys exposed to 600 ppm ethylbenzene for 6 months (Wolf et al. 1956); however, the utility of this study is limited by a general lack of study details (e.g., no

exposure or control data were provided) and the small size of exposure groups (1–2 rabbits or monkeys per group). No histopathological findings clearly attributable to ethylbenzene were observed in respiratory tissue of rats or mice exposed to up to 750 ppm ethylbenzene for 2 years (NTP 1999). Although the incidences of edema, congestion, and hemorrhage observed in male rats in the 750 ppm group were increased relative to control rats, observations were considered to be agonal changes in moribund animals and not directly related to chemical toxicity (NTP 1999).

Cardiovascular Effects. Intermediate and chronic exposure of animals to inhaled ethylbenzene does not appear to produce adverse cardiovascular effects, based on results of histopathological examinations. No adverse histopathological effects were reported in cardiac tissue of rats or mice exposed to 782 ppm or rabbits exposed to 1,610 ppm ethylbenzene for 4 weeks (Cragg et al. 1989). Similarly, no cardiovascular effects were observed in rats or mice exposed to 975 ppm ethylbenzene for 90 days (NTP 1992) or in rats exposed to 2,200 ppm, guinea pigs or rabbits exposed to 1,250 ppm, or monkeys exposed to 600 ppm ethylbenzene for 6 months (Wolf et al. 1956). No adverse histopathological findings were observed in cardiovascular tissues of rats or mice exposed to 750 ppm ethylbenzene for 2 years (NTP 1999).

Gastrointestinal Effects. No adverse effects on the gastrointestinal system have been observed following intermediate or chronic inhalation exposure of animals. No changes in gross appearance or adverse histopathological effects were observed in the intestines of rats and mice exposed to 782 ppm or rabbits exposed to 1,610 ppm ethylbenzene for 4 weeks (Cragg et al. 1989). No adverse histopathological changes in gastrointestinal tissue were observed in rats or mice exposed to ≤975 ppm ethylbenzene for 90 days (NTP 1992) or in rats or mice exposed to ≤750 ppm ethylbenzene for 2 years (NTP 1999).

Hematological Effects. Two studies involving long-term monitoring of workers occupationally exposed to ethylbenzene were located (Angerer and Wulf 1985; Bardodej and Cirek 1988). Angerer and Wulf (1985) reported increased lymphocyte count and decreased hemoglobin concentration in male varnish workers exposed to a mixture of solvents, including ethylbenzene, compared to an unexposed control group. Workers were employed for an average of 8.2 years and exposed to an average ethylbenzene concentration of 1.64 ppm. Average lymphocyte levels increased (41.5–68.8%) and average hemoglobin values decreased (5.2–7.1%) in exposed workers, compared to unexposed controls. However, due to concomitant exposure to other chemicals (xylenes, lead, toluene), the relationship of adverse hematological effects to inhaled ethylbenzene cannot be established. No adverse hematological effects were seen in male workers employed at an ethylbenzene manufacturing facility over a 20-year period, compared to unexposed control workers (Bardodej and Cirek 1988). Although no information on

ethylbenzene concentrations was reported, an estimated concentration of 6.4 mg/m^3 was derived from a mean post-shift in urinary mandelic acid concentration in workers, based on the relationship between ethylbenzene concentrations in air and urinary mandelic acid concentration in a chamber-exposed group (Bardodej and Bardodejova 1988). However, given the low exposure concentration, this study had limited power to detect any effect.

Studies using animal models yield conflicting results regarding hematological effects of inhaled ethylbenzene. Platelet count was significantly decreased in male rats and mean total leukocyte count was significantly increased in female rats exposed to 782 ppm ethylbenzene for 4 weeks; hematological effects were not observed in male or female rats exposed to ≤382 ppm, mice exposed to ≤782 ppm, or rabbits exposed to ≤1,610 ppm (Cragg et al. 1989). Similarly, no hematological effects were observed in female rats exposed to ≤500 ppm ethylbenzene vapor daily for 28 days, based results of complete blood count with differential and assessments of erythrocyte morphology and hemoglobin content (Stump 2004). No adverse hematological effects were observed in rats or mice exposed to 975 ppm ethylbenzene for 90 days (NTP 1992), or in rats exposed to ≤2,200 ppm, guinea pigs or rabbits exposed ≤1,250 ppm, or monkeys exposed to ≤600 ppm ethylbenzene for 6 months (Wolf et al. 1956).

Musculoskeletal Effects. No musculoskeletal effects have been observed in laboratory animals exposed to inhaled ethylbenzene for intermediate or chronic durations. No bone tissue abnormalities were observed upon histopathological examination of tissue from rats and mice exposed to 782 ppm and rabbits exposed to 1,610 ppm for 4 weeks (Cragg et al. 1989). Similarly, no adverse effect on bone tissue was observed in rats or mice exposed to 975 ppm ethylbenzene for 90 days (NTP 1992) or 750 ppm for 2 years (NTP 1999).

Hepatic Effects. No adverse effects on liver function, as measured by serum liver enzyme activities, were observed in male workers employed at an ethylbenzene manufacturing facility over a 20-year period (Bardodej and Cirek 1988). Although no information on ethylbenzene concentrations was reported, an estimated concentration of 6.4 mg/m^3 was derived as described above under hematological effects (Section 3.2.1.3). Given the low exposure concentration, this study had limited the power to detect any effect.

Results of studies in laboratory animals have found various effects on the liver, including induction of cytochrome P-450, changes in liver weight (at least in part related to induction of cytochrome P-450), changes in hepatocyte ultrastructure consistent with induction of smooth endoplasmic reticulum, and

histopathological changes, including hepatocyte necrosis. Increased liver weights, induction of hepatic drug metabolizing enzymes, and changes in hepatocyte ultrastructure (consistent with induction of smooth endoplasmic reticulum) have been observed in rats following acute inhalation exposure to ethylbenzene. Concentration-related increases in absolute and relative liver weights were reported in male rats exposed to ≥400 ppm ethylbenzene for 3–4 days, although no histopathological changes were observed (Ethylbenzene Producers Association 1986a). Increased relative liver weight, increased hepatic concentration of cytochrome P-450, and induction of hepatic microsomal enzymes (NADPH-cytochrome reductase, 7-ethoxycoumarin O-deethylase) were reported in rats exposed to 2,000 ppm ethylbenzene concentrations for 3 days (Toftgard and Nilsen 1982). Similarly, hepatic drug metabolizing enzymes (UDP glucuronyl-transferase, D-glucuronolactone dehydrogenase) were increased in male rats exposed to 50 ppm ethylbenzene for 2 weeks, and ethyoxycoumarin o-deethylase was increased at 300 ppm (Elovaara et al. 1985). Electron microscopy showed changes in hepatocyte ultrastructure consistent with induction of cytochrome P-450 (e.g., smooth endoplasmic reticulum proliferation, slight degranulation of rough endoplasmic reticulum) in rats exposed to 600 ppm ethylbenzene for 2 weeks (Elovaara et al. 1985). Hepatic changes following acute exposure to ethylbenzene are consistent with induction of hepatic microsomal enzymes.

Similar hepatic effects (liver weights, induction of hepatic drug metabolizing enzymes, and changes in hepatocyte ultrastructure) also have been reported in laboratory animals exposed to inhaled ethylbenzene for intermediate exposure durations. Significant increases in relative liver weight were observed in female rats exposed to ≥250 ppm ethylbenzene for 15 days (Saillenfait et al. 2006), rats and mice exposed to 782 ppm ethylbenzene for 4 weeks (Cragg et al. 1989), pregnant and nonpregnant rats and pregnant rabbits exposed to 1,000 ppm ethylbenzene for 3 weeks prior to mating and throughout gestation (NIOSH 1981), and rats and mice exposed to 246 and 740 ppm ethylbenzene, respectively, for 90 days (NTP 1992). Increased liver weight was also observed in rats exposed to 400 ppm, and guinea pigs and monkeys exposed to 600 ppm ethylbenzene for 6 months (Wolf et al. 1956). Hepatic microsomal enzymes (total cytochrome P-450 protein, 7-ethoxycoumarin O-deethylase, aminopyrine N-demthylase) were induced in rats exposed to 50 ppm ethylbenzene for 16 weeks and changes in hepatocyte ultrastructure (e.g., smooth endoplasmic reticulum proliferation, slight degranulation of rough endoplasmic reticulum) in rats exposed to ethylbenzene from 2 to 15 weeks (Elovaara et al. 1985).

Other histopathological findings in animals exposed to inhaled ethylbenzene were moderate to marked hypertrophy of periportal hepatocytes with clear cytoplasm in female rats exposed to ≥250 ppm ethylbenzene for 15 days (the investigators noted that minimal hypertrophy was observed in controls)

(Saillenfait et al. 2006) and a cloudy swelling of hepatocytes of rats exposed to 2,200 ppm for 6 months (Wolf et al. 1956). Slight, statistically significant increases in relative liver weights (≤7% compared to controls) were observed in male and female B6C3F1 mice exposed to 750 ppm, but not 75 ppm, ethylbenzene vapor for 1 or 4 weeks (Stott et al. 2003). Histopathological assessment showed hepatocellular hypertrophy, mitotic figures, and S-phase DNA synthesis in mice exposed to 750 ppm ethylbenzene vapor for 1 or 4 weeks, but serum activities of hepatic enzymes (alanine transaminase, asparatate transpeptidase, alkaline phosphatase, and γ-glutamyl trnaspeptidase) were not elevated compared to controls. No histopathological changes in the liver were observed in rats or mice exposed to 246 and 740 ppm, respectively, for 90 days (NTP 1992).

Chronic exposure of mice, but not rats, to inhaled ethylbenzene for 2 years produced hepatic toxicity, as indicated by histopathological changes (syncytial alterations of hepatocytes, hepatocellular hypertrophy, and hepatocyte necrosis) (NTP 1999). Syncytial alterations (enlarged hepatocytes with multiple nuclei), which were concentration-related in incidence and severity, were observed at in male mice exposed to ≥75 ppm ethylbenzene, and hepatocyte hypertrophy and necrosis were observed in male mice exposed to 750 ppm. In female mice exposed to 750 ppm ethylbenzene for 2 years, the incidence and severity of eosinophilic foci, which was considered to be a preneoplastic lesion, was increased.

Renal Effects. Renal effects of acute and intermediate exposure to inhaled ethylbenzene are primarily limited to minimally adverse effects, including increased kidney weight in rats and mice and induction of microsomal enzymes in rats. However, chronic exposure of male and female rats results in more serious renal effects, including nephropathy, renal tubule hyperplasia, and renal tubular adenomas and carcinomas (see Section 3.2.1.7, Cancer). In addition, effects associated with accumulation of $\alpha_{2\mu}$-globulin and hyaline droplets have been observed in male rats exposed to inhaled ethylbenzene. Accumulation of $\alpha_{2\mu}$-globulin in the renal tubule epithelial cells of male rats is associated with tubular epithelial necrosis, regenerative proliferation, and renal tumors. This accumulation is not observed in female rats, mice, or humans (which lack that protein), or in male rats, which are genetically lacking $\alpha_{2\mu}$-globulin. Adverse effects in male rats associated with renal accumulation of $\alpha_{2\mu}$-globulin are therefore not considered relevant to humans (EPA 1991d). However, since renal toxicity of chronic exposure to inhaled ethylbenzene has been observed in female rats, renal effects associated with ethylbenzene are relevant to humans.

Acute exposure to inhaled ethylbenzene had been reported to produce increases in kidney weight, induce renal microsomal enzymes, and enhance renal hyaline droplets in rats of both sexes. In male rats only,

this accumulation includes $\alpha_{2\mu}$-globulin, but evidently other proteins are involved in females, and probably also in the males. Relative kidney weight was significantly increased (11–20%) in male rats exposed to 2,000 ppm for 2 days (Toftgard and Nilsen 1982) and 1,200 ppm ethylbenzene for 4 days (Ethylbenzene Producers Association 1986a), and in male and female rats exposed to 750 ppm ethylbenzene (6–7%), but not at 75 ppm, for 1 week (Stott et al. 2003). Although no change in renal histopathology accompanied increased kidney weight in rats exposed to 1,200 ppm ethylbenzene for 4 days (Ethylbenzene Producers Association 1986a), increased accumulation of $\alpha_{2\mu}$-globulin and hyaline droplets were observed after 1 week in the kidneys of male rats exposed to 750 ppm ethylbenzene compared to controls (Stott et al. 2003). Renal congestion was reported in rats and mice that died during exposure to 2,400 or 1,200 ppm ethylbenzene, respectively (Ethylbenzene Producers Association 1986a). Induction of renal cytochrome P-450 microsomal enzymes (7-ethoxycoumarin, O-deethylase, UDP glucuronyl-transferase, NADPH-cytochrome c reductase) was reported in rats following a 3-day exposure to 2,000 ppm ethylbenzene (Toftgard and Nilsen 1982).

Renal effects of intermediate-duration exposure to inhaled ethylbenzene are similar to those observed following acute exposure (increased kidney weight, induction of renal microsomal enzymes, and changes associated with accumulation of $\alpha_{2\mu}$-globulin). Several studies have shown that exposure of rats or mice to inhaled ethylbenzene for durations of 4 weeks –7 months increases relative kidney weight (Elovaara et al. 1985; NIOSH 1981; NTP 1999; Stott et al. 2003; Wolf et al. 1956). Concentration-related increases in renal microsomal enzymes (7-ethoxycoumarin O-deethylase, UDP glucuronyl-transferase) and renal glutathione concentration were reported in rats following a 5–16-week exposure to ethylbenzene at concentrations ranging from 50 to 600 ppm (Elovaara et al. 1985). Histopathological changes in the kidney include $\alpha_{2\mu}$-globulin-associated changes (nuclear-size and staining variations and vacuolation or decreased amount of cytoplasm) in male rats exposed to 750 ppm for 4 weeks (Stott et al. 2003) and swelling of the tubular epithelium in rats exposed to 600 ppm ethylbenzene for up to 7 months (Wolf et al. 1956).

Chronic exposure of male and female rats, but not mice, to inhaled ethylbenzene for 2 years resulted in nephropathy and renal tubule hyperplasia (NTP 1999). Although age-related nephropathy was observed in control rats, the severity was increased compared to controls in female rats exposed to ≥75 ppm and male rats exposed to 750 ppm. The incidence of renal tubular hyperplasia (considered as a preneoplastic effect) was increased in male and female rats exposed to 750 ppm. NTP (1999) concluded that ethylbenzene may have exacerbated the development of age-related nephropathy in rats and that renal

tubular lesions were related to exposure. Additional information pertaining to renal carcinogenesis is provided in Section 3.2.1.7.

Endocrine Effects. Adverse endocrine effects, based on histopathological examinations of endocrine tissues, have not been observed in laboratory animals exposed to inhaled ethylbenzene for 4 weeks to 6 months (Cragg et al. 1989; NTP 1992; Wolf et al. 1956), although chronic exposure is reported to produce hyperplasia of the thyroid and pituitary (NTP 1999). Mice exposed to 750 ppm ethylbenzene for 2 years showed an increased incidence of follicular cell hyperplasia in the thyroid gland. In female mice exposed to ≥250 ppm ethylbenzene, the incidences of hyperplasia of the pituitary gland pars distalis were significantly greater than those in the control group. No effects on other endocrine tissues were observed in mice and no effects on any endocrine tissue were observed in rats exposed to 750 ppm ethylbenzene for 2 years (NTP 1999).

Ocular Effects. Ocular effects observed in humans and animals after inhalation exposure to ethylbenzene are presumed to be due to direct contact of the eyes with ethylbenzene vapor. These effects are discussed in Section 3.2.3.2.

Body Weight Effects. Studies in animals examined body weight effects in acute-, intermediate-, and chronic-duration inhalation exposure to ethylbenzene. Mean body weight was not affected in rats or mice exposed to 400 ppm or in rabbits exposed to 2,400 ppm ethylbenzene for 4 days (Ethylbenzene Producers Association 1986a). Rats exposed to 1,200 ppm showed a mean body weight that was lower than in control animals. No effect on body weight was observed in rabbits after 7 days of exposure to 750 ppm (Romanelli et al. 1986).

No changes in body weight were observed in pregnant rats or rabbits exposed to 985 and 962 ppm ethylbenzene, respectively, for 3 weeks prior to mating and throughout gestation (NIOSH 1981). A decrease in body weight gain of 26–48% at weeks 2, 5, and 9, but not at week 16 was observed in male rats exposed to 600 ppm ethylbenzene for 16 weeks (Elovaara et al. 1985). No adverse effect on body weight was observed in rats or mice exposed to 782 ppm or rabbits exposed to 1,610 ppm ethylbenzene for 4 weeks (Cragg et al. 1989). In female rats exposed to up to 500 ppm ethylbenzene daily for 28 days, no effects on body weight were observed (Stump 2004). No effect on body weight was observed in rats and mice exposed to 975 ppm ethylbenzene for 90 days (NTP 1992). Similarly, no biologically significant effect on body weight was observed in rats and mice exposed to concentrations of ethylbenzene of up to 750 ppm for 2 years (NTP 1999).

3.2.1.3 Immunological and Lymphoreticular Effects

Angerer and Wulf (1985) reported increased lymphocyte counts in male varnish workers exposed to a mixture of solvents, including ethylbenzene, compared to an unexposed control group. Workers were employed for an average of 8.2 years and exposed to an average ethylbenzene concentration of 1.64 ppm. Average lymphocyte levels increased (41.5–68.8%) in exposed workers, compared to unexposed controls. However, due to concomitant exposure to other chemicals (xylenes, lead, toluene), the relationship of adverse hematological effects to inhaled ethylbenzene cannot be established.

Mean total leukocyte count was significantly increased in female rats expose to 782 ppm ethylbenzene, but not ≤382 ppm, for 4 weeks (Cragg et al. 1989). Absolute and relative spleen weights were increased in pregnant rats exposed to 1,000 ppm ethylbenzene during pre-mating and gestation or gestation alone, although histopathological changes were not observed (NIOSH 1981). Spleen weight was not affected in rabbits exposed to 1,000 ppm during gestation (NIOSH 1981). No histopathological changes were observed in bone marrow (sternum), lymph nodes, thymic region, or spleen of rats or mice exposed to 782 ppm or rabbits exposed to 1,610 ppm ethylbenzene for 4 weeks (Cragg et al. 1989). In female rats exposed to ethylbenzene at concentrations up to 500 ppm for 6 hours/day, no effects were observed on humoral immunity (as assessed by the IgM antibody-forming response to the T cell-dependent antigen sheep erythrocytes), thymus or spleen weight, or blood leukocyte populations (Stump 2004). No treatment-related effect on the histopathology of several lymphoreticular tissues, including bronchial lymph nodes, regional lymph nodes, mandibular and mesenteric lymph nodes, mediastinal lymph nodes, spleen, or thymus were observed in rats and mice exposed to 975 ppm ethylbenzene for 90 days (NTP 1992) or 750 ppm for 2 years (NTP 1999).

The highest NOAELs for immunological and lymphoreticular effects in each species for intermediate- or chronic-duration exposure are reported in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Symptoms of dizziness accompanied by vertigo have been observed in humans acutely exposed to air concentrations of ethylbenzene ranging from 2,000 to 5,000 ppm for 6 minutes (Yant et al. 1930).

Workers exposed occupationally for a mean of 13 years to solvent mixtures that include ethylbenzene (mean ethylbenzene exposure level 1.8 ppm) showed a 58% incidence of hearing loss compared to

36% in the reference group (Sliwinska-Kowalska et al. 2001). Hearing losses (expressed as increased hearing thresholds) were observed at all frequencies and appeared to range from 3 to 8 dB. The role of ethylbenzene in the observed losses cannot be ascertained from this study given that ethylbenzene was only one of several solvents, most of which were present at mean concentrations 1.5–3.5 times higher than ethylbenzene.

Neurological effects have been observed in several animals following acute-duration exposure to inhaled ethylbenzene, although there is considerable variability in species sensitivity. In general, central nervous system depression is associated with acute exposure to higher concentrations, whereas stimulation of the motor nervous system is associated with lower concentrations. The most serious adverse neurological effect associated with acute- and intermediate-duration inhalation exposure to ethylbenzene is ototoxicity, characterized by deterioration in auditory thresholds and alterations of cochlear morphology.

Clinical signs of general central nervous system depression or increased motor activity have been observed in animals acutely exposed to inhaled ethylbenzene. Moderate activation in motor behavior was observed in rats following a 4-hour inhalation exposure to levels of ethylbenzene ranging from 400 to 1,500 ppm, whereas narcotic effects were observed at higher ethylbenzene concentrations (2,180–5,000 ppm) (Molnar et al. 1986). This study is limited by a lack of methodological detail and appropriate statistical analysis. Central nervous system depression (unconsciousness) and ataxia were observed in guinea pigs exposed to 2,000 ppm ethylbenzene for acute-duration periods (Yant et al. 1930). Salivation, prostration, and/or reduced activity were observed in rats and mice exposed to 2,400 or 1,200 ppm ethylbenzene, respectively, for 4 days (Ethylbenzene Producers Association 1986a). However, rabbits exposed to 2,400 ppm ethylbenzene for the same period showed no adverse behavioral effects. Exposure of mice to ethylbenzene for 20 minutes to ≥2,000 ppm produced changes in posture; decreased arousal and rearing; increased ease of handling; disturbances of gait, mobility, and righting reflex; decreased forelimb grip strength; increased landing foot splay; and impaired psychomotor coordination (Tegeris and Balster 1994). These acute effects were short-lived and more pronounced during exposure than after exposure, with recovery beginning within minutes of removal from the exposure chamber. Sensorimotor reactivity also decreased. Acute exposure of rats and mice to 245 and 342 ppm, respectively (Frantik et al. 1994), resulted in a 30% depression of evoked electrical activity in the brain immediately after exposure.

General signs of neurotoxicity have not been observed in animals exposed to inhaled ethylbenzene for intermediate or chronic durations, although ethylbenzene concentrations evaluated in intermediate- and

chronic-duration studies were lower than those evaluated in acute studies. No behavioral changes, clinical signs of neurotoxicity or histopathological alterations of neurological tissues were observed in rats or mice exposed to concentrations of up to 782 ppm or rabbits exposed to concentrations up to 1,610 ppm ethylbenzene for 4 weeks. Sporadic salivation was noted in rats at doses of ≥382 ppm (Cragg et al. 1989). In a 90-day study (NTP 1992), rats and mice showed no adverse histopathological effects on brain tissue at doses up to 975 ppm. No adverse effects were noted in the brain tissues of rats and mice exposed to concentrations of ethylbenzene of up to 750 ppm for 2 years (NTP 1999).

Ototoxic effects of inhaled ethylbenzene have been observed following acute- or intermediate-duration exposure of rats. Effects are characterized by deterioration in auditory thresholds and alterations of cochlear morphology. Male rats exposed to ethylbenzene at 800 ppm, 8 hours/day for 5 days showed significant deterioration in auditory thresholds (threshold shifts were 10–20 and 17–28 dB using two methods) 1 and 4 weeks after the exposure had ceased (Cappaert et al. 1999). The magnitude of the increase in thresholds did not change between assessments conducted on post-exposure weeks 1 and 4; threshold shifts were evident at all tested frequencies (1–24 kHz). Eight to 11 weeks after exposure, a significant loss (52–66%) of outer hair cells (OHCs) in the organ of Corti in the auditory region corresponding to 11–21 kHz was observed. No loss of inner hair cells (IHCs) was found in the exposed animals (Cappaert et al. 1999). Similarly, auditory threshold shifts (approximately 15–30 dB) and OHC losses (25–75%) were observed 3–6 weeks after exposure in male rats exposed to 400 or 550 ppm ethylbenzene, 8 hours/day for 5 days. Auditory thresholds and OHC counts were not affected in rats exposed to 300 ppm ethylbenzene (Cappaert et al. 2000, 2001). Cappaert et al. (2002) demonstrated a significant species difference in the susceptibility of rats and guinea pigs to the ototoxic effects of ethylbenzene. Guinea pigs exposed to ethylbenzene at 2,500 ppm, 6 hours/day for 5 days did not show auditory deficits or losses in OHCs. There was no loss of IHCs in either species (Cappaert et al. 2002).

Auditory deficits persisted unchanged throughout the 13-week exposure period and the 8-week post-exposure recovery period in rats exposed to ≥400 ppm ethylbenzene (Gagnaire et al. 2007). Histological assessments conducted after the 8-week recovery period showed significant losses in OHCs in rats exposed to ≥200 ppm ethylbenzene, 6 hours/day, 6 days/week for 13 weeks (Gagnaire et al. 2007). IHC losses (14–32%) were observed in rats exposed to 600 and 800 ppm ethylbenzene, but only occasionally in rats exposed to 400 ppm (Gagnaire et al. 2007).

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

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to ethylbenzene.

No adverse effects on reproduction were observed in female rats and rabbits exposed to approximately 100 or 1,000 ppm ethylbenzene for 3 weeks prior to mating and throughout gestation (NIOSH 1981). Reproductive function and outcome was assessed in a 2-generation reproductive toxicity study in rats exposed to 25, 100, or 500 ppm ethylbenzene starting with a pre-mating exposure of ≥70 days and continuing through gestation day 20, lactation day 5–21, and postnatal day 21 (Faber et al. 2006). On lactational days 1–4 for F0 and F1 dams, inhalation exposure was discontinued and oral ethylbenzene (in corn oil at doses of 0, 26, 90, or 342 mg/kg/day) was administered; inhalation exposure was re-initiated on lactational day 5 and maintained for the remainder of the exposure period. Oral exposure on lactational days 1–4 was intended to provide the same maternal blood concentrations as inhalation exposure. Estrous cycle length was significantly reduced in F0 rats in the 500-ppm group (4.0 days vs. 4.4 days in controls), but was not altered in the F1 females. Reproductive parameters (mating or fertility indices, gestation length, number of implantation sites, number of births/litter, and litter size) were not affected in F0 or F1 females (or males, as appropriate) exposed to 25–500 ppm ethylbenzene.

No treatment-related histopathological changes were noted in the testes of rats, mice, or rabbits exposed to concentrations as high as 2,400 ppm ethylbenzene for 4 days (Ethylbenzene Producers Association 1986a). No testicular histopathological abnormalities were reported in rats and mice exposed to 782 ppm and rabbits exposed to ethylbenzene concentrations as high as 1,610 ppm for 4 weeks (Cragg et al. 1989). NTP (1992) reported no effect on sperm or testicular morphology or on the length of the estrous cycle in rats or mice exposed to 975 ppm ethylbenzene for 90 days. Mice showed a decrease in epididymal weight in the 1,000-ppm group; however, this observation was not considered biologically significant since there was no significant difference in spermatid counts, sperm motility, or weight of the caudal epididymis among treated and control animals. Inhalation exposure of male monkeys and rabbits to 600 ppm ethylbenzene for 6 months produced degeneration of germinal epithelium in the testes of one monkey and one rabbit (Wolf et al. 1956). No adverse histopathological effects were seen in the testes of rats or guinea pigs exposed to concentrations up to 1,250 or 600 ppm, respectively, for 6–7 months (Wolf et al. 1956). In a 2-generation reproduction study, no effects were observed on sperm number, motility, and morphology in F0 and F1 rats exposed to 25–500 ppm ethylbenzene (Faber et al. 2006).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species for acute-, intermediate-, and chronic-duration are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to ethylbenzene.

The developmental effects of inhaled ethylbenzene have been studied in rats (NIOSH 1981; Ungváry and Tátrai 1985), mice (Ungváry and Tátrai 1985), and rabbits (NIOSH 1981; Ungváry and Tátrai 1985) exposed during gestation or pre-mating and gestation; rats exposed from pre-gestation through lactation (Faber et al. 2006); and in a 2-generation reproduction study in rats (Faber et al. 2007). Results of studies in rats indicate that ethylbenzene produces reduced fetal weight, skeletal anomalies, and anomalies and delayed development of urogenital tract; skeletal and urogenital anomalies were observed in the presence of maternal toxicity (Faber et al. 2006; NIOSH 1981; Ungváry and Tátrai 1985). Studies conducted by Faber et al. (2006, 2007) and NIOSH (1981) are of high quality and guideline-compliant. However, usefulness of the Ungváry and Tátrai (1985) study is hampered by incomplete descriptions of the results and because an analysis of the results on a per litter basis was not provided.

In rats, continuous inhalation exposure to ethylbenzene on gestational days 7–15 to concentrations ranging from 138 to 552 ppm resulted in fetal resorption and skeletal retardation (Ungváry and Tátrai 1985). Retarded skeletal development was observed in 13, 26, 30, and 35% of fetuses exposed to 138, 276, and 552 ppm ethylbenzene, respectively. Increased incidence of extra ribs and anomalies of the urinary tract (specific effects not reported) were observed in 7% of fetuses at 552 ppm, compared to 1% in controls. Maternal toxicity was reported to be moderate and dose-dependent, but data were not presented. In this same study, the incidence of anomalies of the uropoietic apparatus (not specified) was observed in the offspring of mice exposed to 115 ppm ethylbenzene on gestation days 6–15. Anomalies of the uropoietic apparatus were not observed in other developmental studies (Faber et al. 2006, 2007; Saillenfait et al. 2003, 2006, 2007). In rabbits continuously exposed to ethylbenzene on gestation days 7–20, decreases in female fetal body weights were observed at 115 ppm and an increase in abortions (3/3 does aborted compared to 0/60 in controls) were observed at 230 ppm. The Ungváry and Tátrai (1985) study did not include sufficient details regarding the adverse fetal effects, dictating caution in the interpretation of study findings.

In a NIOSH sponsored study conducted by Andrews et al. (NIOSH 1981), increases in the incidences of fetuses with extra ribs were observed in the offspring of rats exposed to 100 or 1,000 ppm ethylbenzene through gestation day 19 or 1,000 ppm during pre-mating and gestation. The incidence of supernumerary ribs was increased only in the offspring of rats exposed to 1,000 ppm during gestation. Reduced pup crown-rump length and an increased incidence of supernumerary ribs were observed in the offspring of rats exposed to 1,000 ppm during gestation, but not in the offspring of rats exposed to 1,000 ppm during pre-mating and gestation. No other significant increases in major malformations or minor anomalies were observed. There was some evidence of maternal toxicity (increased relative liver, kidney, and spleen weights) in rats exposed to 1,000 ppm ethylbenzene during pre-mating and gestation or gestation only (NIOSH 1981).

Statistically significant reductions in fetal body weight were observed in the offspring of pregnant rats exposed to ≥1,000 ppm ethylbenzene during gestation (Saillenfait et al. 2003, 2006, 2007), but not in rats exposed to 500 ppm (Saillenfait et al. 2003) or 250 ppm (Saillenfait et al. 2006, 2007). A significant increase in the number of fetuses with fetal malformations (mostly skeletal variations) was observed in the offspring of rats exposed to ≥1,000 ppm ethylbenzene (Saillenfait et al. 2003, 2006, 2007). On a per litter basis, a significant increase in the incidence of fetal malformations was observed only at 2,000 ppm (Saillenfait et al. 2003). Maternal toxicity was observed in rats exposed to ≥1,000 ppm, as indicated by significant reductions in maternal weight gain compared to control animals (Saillenfait et al. 2003, 2006, 2007).

Survival from birth to postnatal days (PND) 4 and 21 was not affected in F1 or F2 offspring of pregnant rats exposed to ethylbenzene at 25, 100, or 500 ppm during premating, mating, gestation, and lactation (Faber et al. 2006). A statistically significant delay in balanopreputial separation was observed in F1 males in the 500 ppm group, although the mean age at separation in that group (44.7 days) was similar to that observed in historical controls (44.8 days). No exposure-related macroscopic findings or changes in organ weight in F1 pups necropsied on PND 21 were observed.

Results of a 2-generation reproduction study in rats show that the mean age at acquisition of vaginal patency was significantly reduced in F1 females at 25, 100, and 500 ppm; however, the values in the treated groups (33.3–33.9 days) were similar to the historical control value (33.4 days) in the conducting laboratory (Faber et al. 2006). F2 generation pups (which were not exposed to ethylbenzene by inhalation) did not show differences from controls in the age at preputial separation or vaginal patency

(Faber et al. 2007). Developmental landmarks (pinna detachment, hair growth, incisor eruption, and eye opening) were not affected in F1 male or female pups exposed to 25–500 pm ethylbenzene (Faber et al. 2006); however, in the F2 generation, statistically significant delays in hair growth were observed in males and females in all exposure groups and eye opening was significantly delayed in males the 25 and 100 ppm groups, but not in the 500 ppm group (Faber et al. 2007). Neurodevelopmental tests conducted on subsets of the F2 offspring (Faber et al. 2007) did not show statistically significant differences from controls in a functional observational battery assessment or in fore- or hind-limb grip strength. Although the data suggest an increase in motor activity in F2 males and females in the 25–500 ppm groups on PNDs 13 and 17, there were no statistical differences in motor activity on PNDs 13, 17, and 21 between exposed and control animals (Faber et al. 2007). A statistically significant increase in motor activity was observed on PND 61 in F2 females in the 25 ppm group only. Startle response was not affected in F2 rats of either sex on PND 20 or females on PND 60; F2 males showed statistically lower startle responses, but this was attributed to highly variable and abnormal responses in some control animals. Swimming ability, learning, and memory assessments conducted in a Biel water maze did not reveal any significant effects in F2 animals in any of the exposure groups (Faber et al. 2007). No morphometric or histologic effects in brains of F2 animals were observed from any exposure group on PND 21 or 72 (Faber et al. 2007).

Reduced fetal weight was observed in female rats exposed to 115 ppm during gestation (Ungváry and Tátrai 1985). In the offspring of rabbits exposed to ethylbenzene, no treatment-related effects were observed in fetal size, placental weight, or intrauterine growth retardation and there were no significant incidences of major malformations, minor anomalies, or common variants observed in the absence of maternal toxicity (NIOSH 1981).

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

No association has been found between the occurrence of cancer in humans and occupational exposure to ethylbenzene. No cases of malignancy were observed in workers exposed to ethylbenzene monitored for 20 years (Bardodej and Cirek 1988). No information on ethylbenzene concentrations was reported, although an estimated concentration of 6.4 mg/m^3 was derived as described above under hematological effects (Section 3.2.1.3). However, no clear conclusions can be drawn from this study due to the lack of measured ethylbenzene concentrations. Furthermore, the low exposure concentration limited the power

of this study to detect any effect. No other studies were found regarding cancer effects in humans exposed to ethylbenzene by inhalation.

Information concerning the carcinogenicity of ethylbenzene in animals comes from an NTP-sponsored bioassay in male and female rats and mice exposed to 0, 75, 250, or 750 ppm ethylbenzene for up to 2 years (NTP 1999). NTP (1999) concluded that ethylbenzene showed clear evidence of carcinogenic activity in male rats based on increased incidences of renal tubule neoplasms and testicular adenomas, some evidence of carcinogenic activity in female rats based on increased incidences of renal tubule adenomas, some evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms, and some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular neoplasms (NTP 1999).

Pathological findings in male and female rats exposed to 750 ppm ethylbenzene showed significant increases in the incidence of renal tubule adenoma and adenoma or carcinoma (combined) compared to control animals. An extended histopathological evaluation of the kidneys showed significant increases in the incidence of nephropathy and of renal tubular hyperplasia (a preneoplastic lesion) in male rats exposed to 750 ppm; in female rats, nephropathy was observed at concentrations ≥75 ppm and renal tubular hyperplasia was only observed at a concentration of 750 ppm. In a reevaluation of the histopathology of rat kidneys from the NTP study, Hard (2002) confirmed the NTP (1999) findings and suggested that the increase incidence of kidney tumors in rats in the high-dose group was related to a chemical-induced exacerbation of chronic progressive nephropathy (CPN), with a minor contributing factor in male rats being $\alpha_{2\mu}$-globulin nephropathy. However, in an analysis of the association between CPN and renal tubule cell neoplasms in male F344 rats, Seely et al. (2002) concluded that the association between CPN and renal tubule cell neoplasms is marginal. Results of this analysis suggest that the number of renal tubule cell neoplasms secondary to CPN would be few (Seely et al. 2002). The incidence of interstitial cell adenoma in the testes of males exposed to 750 ppm was significantly greater than in the control group and slightly exceeded the historical control range for inhalation studies. The incidence of bilateral testicular adenoma was also significantly increased in males exposed to 750 ppm.

In male mice, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly greater in males exposed to 750 ppm than in the controls. No significant increased in the incidence of neoplastic lung lesions was observed in female rats. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were

significantly greater in female mice exposed to 750 ppm than in the control group. Hepatocellular adenomas or carcinomas were not observed in male mice.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans following oral exposure to ethylbenzene.

Lethality has been observed in laboratory animals following ingestion of ethylbenzene. The oral LD_{50} for gavage administration of ethylbenzene was reported to be 4,769 mg/kg ethylbenzene in rats (Smyth et al. 1962). In another oral study with rats exposed to ethylbenzene, the LD_{50} was reported to be approximately 3,500 mg/kg ethylbenzene (Wolf et al. 1956). The usefulness of these data is limited since the study methodology was not provided.

An oral LD_{50} value for rats is recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located describing respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or gastrointestinal, musculoskeletal, endocrine, dermal, ocular, body weight, or metabolic effects in animals after oral exposure to ethylbenzene.

The highest NOAEL values and all reliable LOAEL values are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. No clinical signs of respiratory effects or histopathological findings in respiratory tissues were observed in male and female rats exposed to 750 mg/kg/day by gavage for 4 or 13 weeks (Mellert et al. 2007). No respiratory effects were observed in female rats orally exposed to 680 mg/kg ethylbenzene by gavage for 6 months (Wolf et al. 1956). The utility of this study is limited because of poor protocol description.

Table 3-2 Levels of Significant Exposure to Ethylbenzene - 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 (Carworth-Wistar)	once (G)				4769 M (LD50)	Smyth et al. 1962	
Neurological								
2	Rat (SD)	1 x/d 5 d/wk 2 wk (G)				900 M (complete loss of outer hair cells in cochlea)	Gagnaire and Langlais 2005	
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat (Wistar)	4 wk 7 d/wk 2 x/d (GO)	Resp	750			Mellert et al. 2007	
			Cardio	750				
			Hemato	750				
			Hepatic	75 M	250 M (increased absolute and relative liver weights, increased incidence of centrilobular hepatocyte hypertrophy)			
			Renal	75 M	250 M (hyaline droplet nephropathy)			

Table 3-2 Levels of Significant Exposure to Ethylbenzene - 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
4	Rat (Wistar)	13 wk 7 d/wk 2 x/d (GO)	Resp	750			Mellert et al. 2007	
			Cardio	750				
			Hemato	250	750 (increased mean corpuscular volume in males and females, decreased platelet counts in females)			
			Hepatic	75[b]	250 (increased serum liver enzymes in males, increased absolute and relative liver weights in males and females, increased incidence of centrilobular hepatocyte hypertrophy in males and females)			
			Renal	75 M	250 M (hyaline droplet nephropathy)			

Table 3-2 Levels of Significant Exposure to Ethylbenzene - 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
5	Rat	6 mo 5 d/wk 1 x/d (GO)	Hemato	680 F			Wolf et al. 1956	Quality of study is poor, with inadequate descriptions of study methods and results.
			Hepatic	136 F	408 F (increased liver weight; cloudy swelling of parenchymal liver cells)			
			Renal	136 F	408 F (increased kidney weight; cloudy swelling of kidney tubular epithelium)			
Neurological								
6	Rat (CD)	2 x/d 13 wk (G)		500			Barnett 2006	Based on negative findings for functional observational battery and motor activity assessments and for histopathology to neurological tissues
7	Rat (Wistar)	4 wk 7 d/wk 2 x/d (GO)		750			Mellert et al. 2007	

Table 3-2 Levels of Significant Exposure to Ethylbenzene - 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
8	Rat (Wistar)	13 wk 7 d/wk 2 x/d (GO)		750			Mellert et al. 2007	NOAEL based on absence of histopathological findings of neurological tissues and negative findings for assessment of motor activity and FOB.
Reproductive								
9	Rat (Wistar)	4 wk 7 d/wk 2 x/d (GO)		750			Mellert et al. 2007	
10	Rat (Wistar)	13 wk 7 d/wk 2 x/d (GO)		750			Mellert et al. 2007	NOAEL based on absence of histopathological findings of reproductive tissues.

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

b Used to derive an intermediate-duration oral MRL of 0.4 mg/kg/day based on a BMDL using an internal dose metric to simulate time averaged liver concentration of ethylbenzene (6.61 µmol/L); a human equivalent dose (HED) of the BMDL was estimated using a human PBPK model. The BMDL(HED) (10.68 mg/kg/day) was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Cardio = cardiovascular; d = day(s); F = Female; (G) = gavage; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

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

Acute (≤14 days)

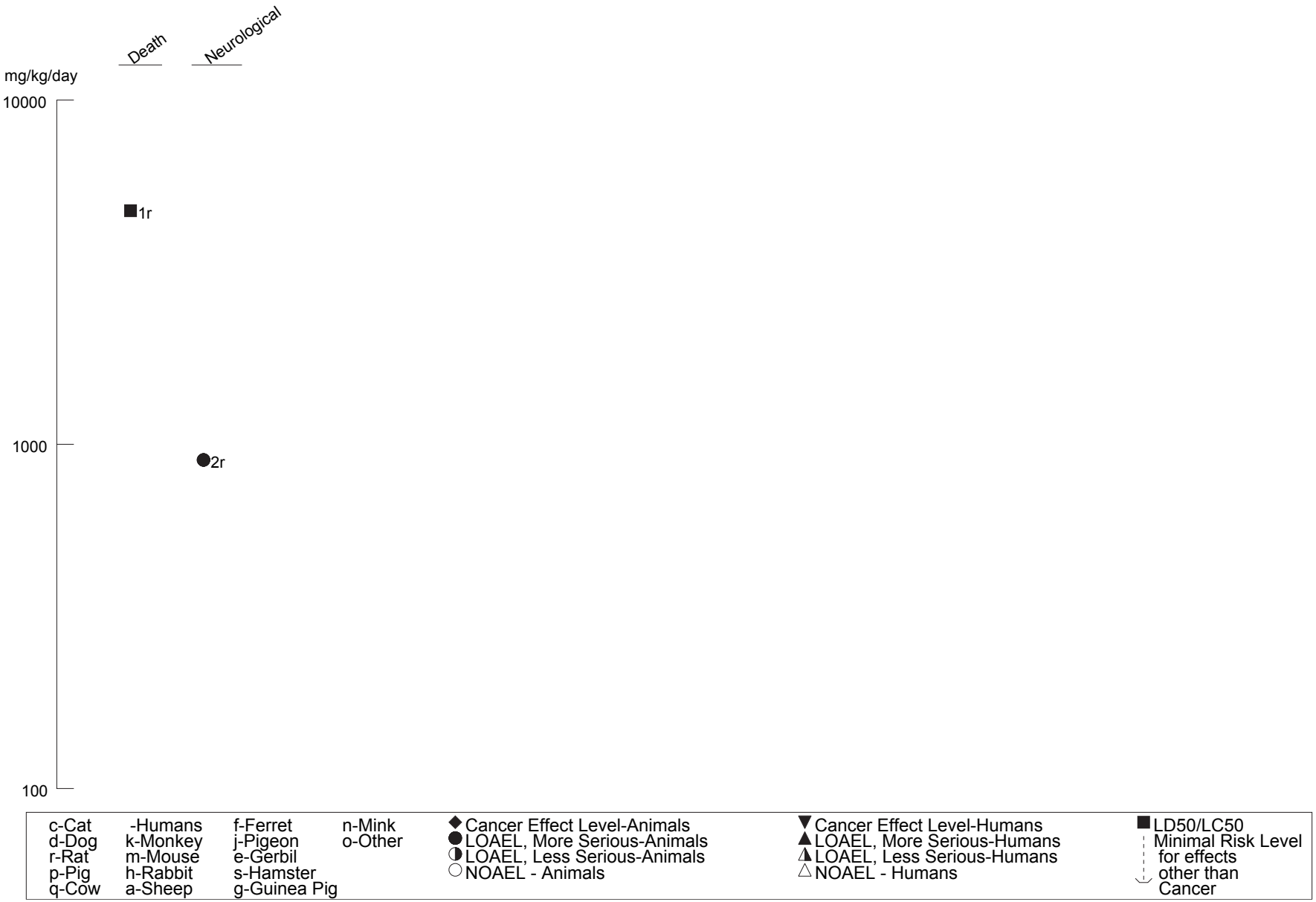
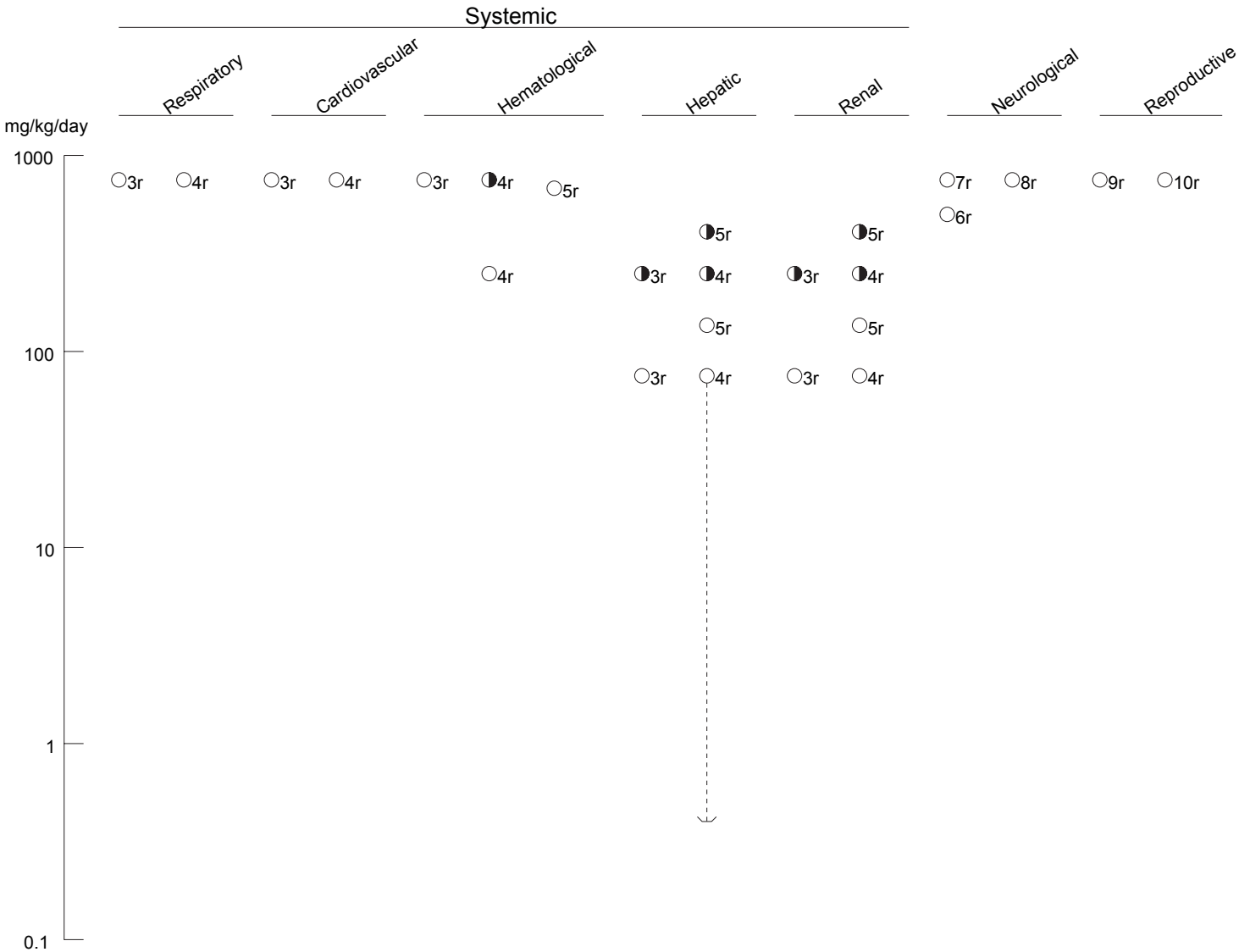


Figure 3-2 Levels of Significant Exposure to Ethylbenzene - Oral *(Continued)*

Intermediate (15-364 days)



Cardiovascular Effects. No histopathological findings were made in cardiac tissue from male and female rats exposed to 750 mg/kg/day by gavage for 4 or 13 weeks (Mellert et al 2007) or from female rats exposed to 13.6–680 mg/kg via gavage for 6 months (Wolf et al. 1956)

Hematological Effects. Decreased platelet count was observed in females administered 750 mg/kg/day and increased mean corpuscular volume was observed in males and females exposed to ≥250 mg/kg/day ethylbenzene by gavage for 13 weeks (Mellert et al 2007). No effects on hematological parameters were observed in rats treated for 4 weeks (Mellert et al. 2007). No adverse effects on bone marrow counts or histopathology were reported in female rats orally exposed to 13.6–680 mg/kg ethylbenzene by gavage for 6 months (Wolf et al. 1956). The usefulness of this study is limited by the poorly described and limited results that were provided.

Hepatic Effects. Effects indicative of liver toxicity were observed in male and female rats exposed to oral ethylbenzene for 4 and 13 weeks (Mellert et al. 2007). After 4 weeks of exposure, observed effects consistent with hepatotoxicity included increased absolute and relative liver weights (≥250 mg/kg/day in males and 750 mg/kg/day in females), increased incidence of hepatocyte centrilobular hypertrophy (≥250 mg/kg/day in males and 750 mg/kg/day in females), and increase serum liver enzyme activity (alanine aminotransferase) (750 mg/kg/day in males and females) (Mellert et al. 2007). After 13 weeks of exposure, increased activity of serum liver enzymes (alanine aminotransferase and γ-glutamyl transferase) in males (≥250 mg/kg/day) and females (750 mg/mg/day), increased absolute and relative liver weights (≥250 mg/kg/day in males and females), and a dose-related increase in the incidence of centrilobular hepatocyte hypertrophy (≥250 mg/kg/day in males and females) were observed. Increased bilirubin (≤250 mg/kg/day in males and 750 mg/kg/day in females), total protein (750 mg/kg/day in females), albumin (750 mg/kg/day in males and females), globulins (750 mg/kg/day in females), and cholesterol (≤250 mg/kg/day in males and females), and decreased prothrombin time (750 mg/kg/day in males and ≥250 mg/kg/day in females) were considered by study investigators as adaptive effects in the liver. In males in the 75 mg/kg/day group, relative liver weight was significantly increased by (4% compared to controls); however, no histopathological changes, or increases in absolute liver or serum liver enzyme activities were observed at this dosage. Given that ethylbenzene is a microsomal enzyme inducer, and the absence of histopathology and other evidence of liver injury at the 75 mg/kg/day dosage, the small increase in relative liver weight in male rats was at this dosage not considered evidence for an adverse effect on the liver (Mellert et al. 2007). Histopathological changes characterized by cloudy swelling of parenchymal cells of the liver and an increase in liver weight were observed in female rats administered 408 mg/kg/day for 6 months (Wolf et al. 1956). No other hepatic changes were reported. No liver effects

were observed in female rats administered 136 mg/kg/day. No conclusions could be drawn from these results because of serious weaknesses in the methodology and reporting of the data, including incidence data and statistical analyses.

Renal Effects. Renal effects in males administered ethylbenzene by gavage for 13 weeks included increased serum creatinine (750 mg/kg/day), increased incidences of transitional epithelial cells and granular and epithelial cell casts in the urine (≥250 mg/kg/day), increased absolute and relative kidney weights (≥250 mg/kg/day), and a dose-related increase in severity of hyaline droplet nephropathy (≥250 mg/kg/day) (Mellert et al. 2007). Adverse renal effects in males were most likely related to accumulation of α2μ-globulin accumulation, and, therefore, considered not relevant to humans. Similar renal findings were observed in male rats exposed for 4 weeks (administered ethylbenzene by gavage for 13 weeks). Absolute kidney weight was significantly increased by 7 and 13% in females administered 250 and 750 mg/kg-day, respectively, compared to controls. However, since no histopathological findings or alterations in urinalysis parameters were observed, increased kidney weight in females was not considered evidence for renal toxicity in female rats. The only animal study that investigated renal effects following ethylbenzene exposure involved female rats administered 13.6–680 mg/kg/body weight ethylbenzene by gavage for 6 months (Wolf et al. 1956). Histopathological changes characterized as cloudy swelling of the tubular epithelium in the kidney and an increase in kidney weight were observed at the 408 mg/kg/day dose level. No other renal changes were reported. As in hepatic effects, no conclusions could be drawn from these results because of serious weaknesses in the methodology and reporting of the data (e.g., no data on the number of animals with renal effects). Furthermore, no statistical analysis was performed.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following oral exposure to ethylbenzene.

Absolute and relative thymus weights were significantly decreased in females treated with ≥250 mg/kg/day for 13 weeks, but no histopathological findings were observed (Mellert et al. 2007). Therefore, effects were not considered adverse.

3.2.2.4 Neurological Effects

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

Significant ototoxic effects were observed in male rats administered 900 mg/kg/day (the only dose tested) by gavage for 2 weeks (Gagnaire and Langlais 2005). The authors reported an almost complete loss of the three rows of OHCs in the organ of Corti 10 days after the last exposure to ethylbenzene. This study did not have a control group to clearly establish the magnitude of the effects relative to unexposed animals; nevertheless, this study showed that the losses observed in ethylbenzene-exposed animals were among the highest observed among 21 organic solvents tested (Gagnaire and Langlais 2005). No ethylbenzene-related behavioral changes were observed in female rats administered 13.6–680 mg/kg/day ethylbenzene by gavage for 6 months (Wolf et al. 1956). No other parameters were investigated. The utility of this study is limited because the monitored behavioral changes were not reported, and the study protocol was poorly described.

In male and female rats exposed to 75–750 mg/kg/day ethylbenzene by gavage for 13 weeks, no neurological effects were observed, based on negative results of motor activity tests and a functional observational battery (FOB) (Mellert et al. 2007). Similarly, no neurological effects were observed in male or female rats admininistered 50–500 mg/kg/day ethylbenzene by gavage for 13 weeks, based on negative findings for FOB and motor activity assessments and for histopathology to neurological tissues (Barnett 2006). However, assessments of ototoxicity were not conducted in these studies.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to ethylbenzene.

The only available reproduction study reported that acute oral exposure to 500 or 1,000 mg/kg ethylbenzene decreases peripheral hormone levels and may block or delay the estrus cycle in female rats during the diestrus stage (Ungváry 1986). Decreased levels of hormones, including luteinizing hormone, progesterone, and 17 β-estradiol, were accompanied by uterine changes, which consisted of increased stromal tissue with dense collagen bundles and reduced lumen. No dose response was noted. The study is limited by the absence of statistical analysis of the data.

No histopathological findings of reproductive tissues were observed in male and female rats exposed to 750 mg/kg/day by gavage for 4 or 13 weeks (Mellert et al. 2007).

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following oral exposure to ethylbenzene.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to ethylbenzene.

The carcinogenicity of ethylbenzene by the oral route has been evaluated in a chronic-duration study in Sprague-Dawley rats (Maltoni et al. 1985). A statistically significant increase in total malignant tumors was reported in females and in combined male and female groups exposed to 500 mg kg/day via gavage for 104 weeks and observed until after week 141. No data on specific tumor type were presented, only one dose was tested, and no information on survival was provided.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding lethal effects in humans following only dermal exposure to ethylbenzene. Matsumoto et al. (1992) reported the case of a 44-year-old man who died 9 days after being massively exposed to gasoline (which contained ethylbenzene) dermally and by inhalation for ≥10 hours.

The dermal LD_{50} in rabbits exposed to liquid ethylbenzene (applied to clipped skin subsequently covered with an impervious plastic film) was calculated to be 15,433 mg/kg/body weight (Smyth et al. 1962). No additional studies were located regarding death in animals following dermal exposure to ethylbenzene.

3.2.3.2 Systemic Effects

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

The systemic effects observed after dermal exposure to ethylbenzene are discussed below. The highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 3-3.

Dermal Effects. No studies were located regarding dermal effects in humans following dermal exposure to ethylbenzene.

Liquid ethylbenzene applied directly to the skin of an unspecified number of rabbits caused irritation characterized by reddening, exfoliation, and blistering (Wolf et al. 1956). Mild dermal irritation (grade 2 on a scale of 10) was also noted in New Zealand White rabbits 24 hours after application of ethylbenzene to clipped skin (Smyth et al. 1962).

Ocular Effects. Ocular effects observed in humans and animals after inhalation exposure are assumed to be due to exposure of the mucous membranes of the eye to ethylbenzene vapor. Volunteers reported eye irritation and burning, and profuse lacrimation, which gradually decreased with continued exposure to 1,000 ppm for 1–6 minutes (Yant et al. 1930). Upon entering the chamber with an ethylbenzene concentration of 2,000 or 5,000 ppm, the volunteers also experienced severe eye irritation. Cometto-Muñiz and Cain (1995) reported eye irritation in humans after exposure to ethylbenzene vapor. Eye irritation was observed at 10,000 ppm.

Liquid ethylbenzene applied directly to the eyes of rabbits for an unspecified duration caused slight irritation of conjunctival membranes (Wolf et al. 1956) and slight corneal injury (Smyth et al. 1962; Wolf et al. 1956).

Irritant effects from exposure to ethylbenzene vapor have been reported in animals. Tegeris and Balster (1994) reported lacrimation and palpebral closure in mice after 20 minutes of exposure to 2,000 ppm ethylbenzene. Eye irritation was observed in guinea pigs exposed to 1,000 ppm for 8 minutes, and in animals exposed to 2,000, 5,000, and 10,000 ppm for 480, 30, and 10 minutes, respectively (Yant et al. 1930). Lacrimation was observed in rats exposed to 1,200 ppm ethylbenzene and in mice and rabbits exposed to 400 ppm ethylbenzene for 4 days (Ethylbenzene Producers Association 1986a). After 4 weeks of exposure to 382 ppm, rats showed sporadic lacrimation, whereas mice and rabbits showed no ocular effects at 782 and 1,610 ppm, respectively (Cragg et al. 1989). No ocular effects were seen in rats or mice after a 13-week exposure to 975 ppm ethylbenzene (NTP 1992).

Table 3-3 Levels of Significant Exposure to Ethylbenzene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
ACUTE EXPOSURE									
Death									
Rabbit (New Zealand)	24 hr					15433 M mg/kg/day	(LD50)	Smyth et al. 1962	
Systemic									
Rabbit (New Zealand)	24 hr	Dermal		8.67 mg	(grade 4 skin irritation)			Smyth et al. 1962	
INTERMEDIATE EXPOSURE									
Systemic									
Rat (F344/N)	13 wk 5 d/wk 6 hr/d	Ocular	975 B ppm					NTP 1992	
Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Ocular	975 B ppm					NTP 1992	

B = males and females; d = day(s); hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; ppm = parts per million; wk = week(s)

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

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

Holz et al. (1995) reported no increase in sister chromatid exchanges, DNA adduct formation, micronuclei, or DNA single-strand breaks in the peripheral lymphocytes of workers exposed to low levels of ethylbenzene and other aromatic hydrocarbons (benzene, toluene, and xylene) in a styrene plant. Chromosomal aberrations were observed in peripheral blood lymphocytes of workers concomitantly exposed to ethylbenzene (0.2–13.1 mg/m^3) and benzene (0.4–15.1 mg/m^3) (Sram et al. 2004). Although a reduction in exposure (reduced ethylbenzene and benzene concentrations not reported) reduced chromosomal aberrations, due to concomitant exposure to benzene, an association between chromosomal damage and ethylbenzene exposure cannot be established. No significant alterations in micronuclei formation were observed in peripheral blood erythrocytes of B6C3F1 mice exposed to 500–1,000 ppm ethylbenzene 6 hours/day, 5 days/week for 13 weeks (NTP 1992, 1999) or in polychromatic erythrocytes in the bone marrow of NMRI mice administered two daily doses of 0.37–0.75 mL/kg via intraperitoneal injection (Mohtashamipur et al. 1985). Similarly, inhalation exposure of B6C3F1 mice to 375–1,000 ppm ethylbenzene for 6 hours did not induce DNA repair (as assessed by unscheduled DNA synthesis) in hepatocytes (Clay 2001). The *in vivo* genotoxicity data in laboratory animals are shown in Table 3-4.

The genotoxic potential of ethylbenzene has been investigated primarily using *in vitro* assays in *Salmonella typhimurium*, *Escherichia coli*, *Saccharomyces cerevisiae*, Chinese hamster ovary cells, mouse lymphoma cells, Syrian hamster embryo cells, and human lymphocytes. Results of these *in vitro* genotoxicity studies are shown in Table 3-5. The available data indicate that ethylbenzene is not mutagenic in bacteria (Dean et al. 1985; Degirmenci et al. 2000; Florin et al. 1980; Kubo et al. 2002; Nestmann et al. 1980; NTP 1986, 1999; Zeiger et al. 1992) or yeast cells (Dean et al. 1985; Nestmann and Lee 1983) in the presence or absence of metabolic activation. Ethylbenzene was found to induce forward

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

Species (test system)	End point	Results	Reference
B6C3F1 mice (inhalation exposure 6 hours/day, 5 days/week for 13 weeks)	Micronuclei formation in peripheral blood erythrocytes	–	NTP 1992, 1999
NMRI mice (intraperitoneal injection)	Micronuclei formation in polychromatic bone marrow erythrocytes	–	Mohtashamipur et al. 1985
B6C3F1 mice (inhalation 6 hours)	Unscheduled DNA synthesis in hepatocytes	–	Clay 2001

– = negative result; DNA = deoxyribonucleic acid

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

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (plate incorporation assay)	Gene mutation	–	–	Dean et al. 1985[a]; Florin et al. 1980[b]; Nestmann et al. 1980[c]
S. tymphimurium (plate incorporation assay; strains TA87, TA98, TA100, TA1537; TA1538)	Gene mutation	–	–	NTP 1986[d]
S. tymphimurium (plate incorporation assay; strains TA97, TA98, TA100, TA1535)	Gene mutation	–	–	Zeiger et al. 1992[d] (results also published in NTP 1992, 1999)
Escherichia coli WP_2, WP_2uvrA	Gene mutation	–	–	Dean et al. 1985[a]
Eukaryotic organisms:				
Saccharomyces cerevisiae JD1 gene conversion assay	Gene mutation	–	–	Dean et al. 1985
S. cerevisiae Dy, XV185-14C	Gene mutation	–	No data	Nestmann and Lee 1983
Mammalian cells:				
Mouse lymphoma cells	Gene mutation	No data	+	McGregor et al. 1988 (results also published in NTP 1992, 1999)
Mouse lymphoma cells	Gene mutation	–	–	Seidel et al. 2006
Mouse lymphoma cells	Gene mutation	–	–	Wollny 2000
Rat liver (RL4) epithelial type cells	Chromosome damage	–	–	Dean et al. 1985
Chinese hamster ovary cells	Chromosome damage	–	–	NTP 1992, 1999
Syrian hamster embryo cells	Micronuclei formation	No data	+	Gibson et al. 1997
Human lymphocytes	Sister chromatid exchange	Not applicable	±[e]	Norppa and Vainio 1983a
Chinese hamster ovary cells	Sister chromatid exchange	–	–	NTP 1986, 1992, 1999
Syrian hamster embryo cells	Cell transformation	No data	+	Kerckaert et al. 1996

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

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human lymphocytes	DNA single strand breaks	No data	+	Chen et al. 2008
Human lymphocytes	DNA double strand breaks	No data	–	Chen et al. 2008

[a]Concentrations of ethylbenzene tested: 0, 0.2, 2, 20, 500, or 2,000 µg/plate (>99% pure)
[b]Concentrations of ethylbenzene tested: 0, 3, 31, 318, or 3,184 µg/plate (0, 0.03, 0.3, 3, or 30 µmole/plate)
[c]Concentrations of ethylbenzene tested: 0.4 mg/plate
[d]Concentrations of ethylbenzene tested: 0, 10, 33, 110, 333, 666, or 1,000 µg/plate
[e]Also cytotoxic.

— = negative result; + = positive result; ± = weakly positive

mutations in mouse lymphoma cells at 80 mg/L without metabolic activation (McGregor et al. 1988; results also reported in NTP 1992, 1999); this concentration was near the lethal concentration of 100 mg/L. Similarly, no alterations in the occurrence of forward mutations in mouse lymphoma cells (with or without activation) were observed at concentrations of ≤50 mg/L (Seidel et al. 2006). A third study examining the occurrence of forward mutations in mouse lymphoma cells (Wollny 2000) found a positive response at cytotoxic concentrations (34.4 and 68.8 µg/mL without metabolic activation and 825 µg/mL with activation); however, two replications of the experiment failed to find a positive mutagenic response. A weak positive response was observed when ethylbenzene was tested for sister chromatid exchanges in human lymphocytes (Norppa and Vainio 1983a); however, the positive response was only observed at a cytotoxic concentration. Ethylbenzene also failed to induce sister-chromatid exchanges in Chinese hamster ovary cells (NTP 1986, 1999) or chromosomal aberrations in Chinese hamster cells (NTP 1986, 1999) or rat liver cells (Dean et al. 1985). A positive dose-related increase in the occurrence of micronuclei formation were observed in Syrian hamster embryo cells tested at ethylbenzene concentrations of 25–200 µg/mL (Gibson et al. 1997). A significant increase in morphological cells transformations was also observed in Syrian hamster embryo cells exposed to 150 or 200 µg/mL for 7 days (Kerckaert et al. 1996); the 200 µg/mL concentration resulted in significant cytotoxicity. In this same study, no significant alterations the percent cell transformations were observed when the cells were incubated with ethylbenzene for 24 hours. A series of studies conducted by Chen et al. (2008) evaluated the potential of ethylbenzene to induce DNA damage in human lymphocytes. A significant increase in single strand breaks was observed at 100 and 200 µM; no alterations in double strand breaks were found at 200 µM. The study also found a significant decrease in DNA damage in cells pre-treated with spin traps, suggesting that the DNA damage may be due to the generation of free radicals.

In general, the results of available *in vivo* and *in vitro* genotoxicity studies suggest that ethylbenzene is not genotoxic. Excluding studies that found results at cytotoxic or near cytotoxic concentrations, a few studies have found positive results. The significance of these positive findings is not known.

3.4 TOXICOKINETICS

Ethylbenzene is absorbed from the lungs, gastrointestinal tract, and through the skin. Absorbed ethylbenzene is rapidly eliminated (blood $t_{1/2} \leq 1$ hour) by metabolism and excretion of metabolites. The major metabolic pathways are side chain and ring hydroxylation with subsequent formation of O-glucuronide and sulfate conjugates. Conjugates, mandelic acid and phenylglyoxylic acid are the

primary excreted metabolites. The distribution of ethylbenzene to tissues has been modeled as a flow-limited process (i.e., clearance from blood to tissues can be predicted by tissue blood flow) with rapid equilibrium achieved between blood and tissues. Measured blood:tissue partition coefficients in the rat are approximately as follows: fat, 36; liver, 2; and muscle, 0.6. These values predict the same order for tissue concentrations for any given blood concentration; however, this order has not been verified experimentally with simultaneously measured blood and tissue ethylbenzene concentrations *in vivo*.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Inhalation studies in humans demonstrate that ethylbenzene is rapidly absorbed via this route (Bardodej and Bardodejova 1970; Gromiec and Piotrowski 1984; Knecht et al. 2000; Tardif et al. 1997). A steady-state blood:alveolar air concentration ratio of approximately 30 was achieved within 1 hour of initiating exposure (Tardif et al. 1997). Volunteers exposed for 8 hours to ethylbenzene at concentrations of 23–85 ppm were shown to retain 64% of the inspired vapor, with only trace amounts detected in expired air at the end of the exposure period (Bardodej and Bardodejova 1970). Another inhalation study that involved humans exposed to similar levels of ethylbenzene demonstrated mean retention rates of 49% (Gromiec and Piotrowski 1984). The differences may be attributable to human variability in absorption rates although they could also be due to differences in methodology.

An initial concentration of ethylbenzene in blood of 2.6 µg/mL and a half-life of 27.5 hours were estimated in a 44-year-old man who died after a massive inhalation and dermal exposure of ≥10 hours to gasoline (Matsumoto et al. 1992). This absorption value may have been slightly overestimated, however, because possible contributions from dermal exposure were not addressed.

In a study conducted in Italy, blood concentrations of ethylbenzene in non-smoking policemen working as traffic wardens showed no significant differences between before and after work shift values or from blood ethylbenzene concentrations in policemen working indoors (Fustinoni et al. 1995). Indoor and outdoor mean air concentrations (measured by personal air samplers) were 21 and 37 mg/m^3, respectively. Before and after shift blood ethylbenzene concentrations were 140 and 163 ng/L in indoor workers, respectively, and were 158 and 184 ng/L in outdoor workers, respectively.

Ethylbenzene concentrations in whole blood collected from workers at the end of their work shifts correlated significantly with the average concentrations of occupational exposure to ethylbenzene (Kawai

et al. 1992). The maximum ethylbenzene concentration in air in the workplace was 5 ppm (Kawai et al. 1992).

Inhalation studies in animals exposed to ethylbenzene showed results similar to those found in humans (Chin et al. 1980b; Freundt et al. 1989; Fuciarelli 2000; Romer et al.1986; Tardif et al. 1997). Harlan-Wistar rats rapidly absorbed radiolabeled ethylbenzene during respiration, with a retention rate of 44% (Chin et al. 1980b). This absorption value may have been slightly overestimated, however, because possible contributions from dermal exposure were not addressed. Concentrations of ethylbenzene in the blood of rats and guinea pigs exposed to ethylbenzene at 550 ppm for 8 hours reached 23 and 3 μg/mL, respectively. Ethylbenzene concentrations in blood after the last of three daily exposures (8 hours each) had diminished to 6 μg/mL in rats and to <2 μg/mL in guinea pigs (Cappaert et al. 2002). In mice, steady-state blood ethylbenzene concentrations achieved within 2 hours of initiating inhalation exposures were approximately 0.71 mg/L at 75 ppm, 2.3 mg/L at 200 ppm, and 20 mg/L at 500 ppm (Charest-Tardif et al. 2006). These data indicate that the disposition of inhaled ethylbenzene between guinea pigs may be different from that in rats and mice. Ethylbenzene concentrations in blood in adult rats and their offspring increased at a rate that was greater than proportional to dose (Faber et al. 2006). Ethylbenzene levels in maternal blood, collected on PND 22, after a 6-hour exposure to 25, 100, or 500 ppm, were 0.11, 0.56, and 11 mg/L, respectively. The mean concentrations in the blood of pups (males/females), culled from the dams sampled above, in the 25-, 100-, and 500-ppm groups were 0.021/0.025, 0.26/0.24, and 11.4/12.7 mg/mL, respectively (Faber et al. 2006).

No studies describing factors specifically affecting absorption of ethylbenzene following inhalation exposure were available.

3.4.1.2 Oral Exposure

No studies were located regarding the absorption of ethylbenzene in humans following oral exposure. Studies in animals, however, indicate that ethylbenzene is quickly and effectively absorbed by this route. Recovery of ethylbenzene metabolites in the urine of rabbits administered a single dose of 593 mg/kg was between 72 and 92% of the administered dose 24 hours following exposure (El Masry et al. 1956). Similarly, 84% of the radioactivity from a single oral dose of 30 mg/kg ethylbenzene administered to female rats was recovered within 48 hours (Climie et al. 1983). Ethylbenzene was detected at 0.49, 3.51, and 18.28 mg/L in maternal blood of rats 1 hour after the last of four daily administrations of 26, 90, or 342 mg/kg/day (distributed over three equal doses), respectively; however, ethylbenzene was not detected

(limit of detection: 0.006 mg/L) in blood of weanlings culled from the same dams (Faber et al. 2006). It is unclear if the latter finding is due to low transfer of ethylbenzene to milk or if the 1-hour exposure-to-sampling time-lapse was too long to allow detection of ethylbenzene.

3.4.1.3 Dermal Exposure

Studies in humans dermally exposed to liquid ethylbenzene demonstrate rapid absorption through the skin, but absorption of ethylbenzene vapors through the skin appears to be minimal (Dutkiewicz and Tyras 1967; Gromiec and Piotrowski 1984). Absorption rates of 24–33 mg/cm^2/hour and 0.11–0.23 mg/cm^2/hour have been measured for male subjects exposed to liquid ethylbenzene and ethylbenzene from aqueous solutions, respectively (Dutkiewicz and Tyras 1967). The average amounts of ethylbenzene absorbed after volunteers immersed one hand for up to 2 hours in an aqueous solution of 112 or 156 mg/L ethylbenzene were 39.2 and 70.7 mg ethylbenzene, respectively. These results indicate that skin absorption could be a major route of uptake of liquid ethylbenzene or ethylbenzene in water. In contrast, ethylbenzene metabolite levels in urine following dermal exposure to 150–300 ppm (650–1,300 mg/m^3) ethylbenzene vapors for two hours did not differ from values taken prior to exposure, indicating minimal, if any, dermal absorption of ethylbenzene vapors (Gromiec and Piotrowski 1984).

Susten et al. (1990) conducted *in vivo* percutaneous absorption studies of ethylbenzene in mice. Results showed total absorption (sums of radioactivity found in the excreta, carcass, skin application site, and expired breath) was 3.4% of the nominal dose. The total percentage recovered (includes wipe of skin area, ethylbenzene 0.03%) was 95.2%. The amount of ethylbenzene absorbed at an estimated contact time of 5 minutes was 148.55 µg with an absorption rate of 37 µg/cm^2/minute.

The volumes of ethylbenzene absorbed in rats treated dermally for 24 hours with aqueous solutions of ethylbenzene (neat [99% pure], saturated, 2/3 or 1/3 saturated), were 0.24, 0.20, 0.18, and 0.17 mL, respectively (Morgan et al. 1991). Peak blood level during exposure to neat ethylbenzene was reported at 5.6 µg/mL, attained after 1 hour of exposure, which decreased during the remainder of the exposure period. The concentration of ethylbenzene in the blood was highest after exposure to saturated aqueous solutions, followed by the 2/3 and 1/3 saturated solutions.

Results of dermal penetration studies in excised rat skin indicate that the penetration rate of pure ethylbenzene (Tsuruta 1982) is faster than that of ethylbenzene from JP-8 jet fuel (McDougal et al. 2000). The penetration rates of pure liquid ethylbenzene following 3-, 4-, and 5-hour exposure durations in rat

skin were approximately 2.38, 3.12, and 3.22 µg/cm^2/hour (calculated by ATSDR from reported data on exposure area, exposure time, and mass transfer); these rates are substantially lower than the rate of dermal absorption determined for humans (Tsuruta 1982). This might be attributed to differences between *in vitro* and *in vivo* testing and/or differences in rat versus human skin. McDougal et al. (2000) reported an ethylbenzene flux of 0.377 µg/cm^2/hour (0.0004 mg/cm^2/hour) for ethylbenzene and a permeability coefficient of 3.1x10^{-4} cm/hour during a 4-hour period in excised rat skin which had received 2 mL of JP-8 fuel containing approximately 1,200 µg ethylbenzene/mL fuel (0.15% w/w). It was recognized that the choice of vehicle (JP-8) could affect dermal penetration of ethylbenzene. The steady state flux, permeability, and diffusivity values of ethylbenzene in pig skin treated with JP-8 *ex vivo* were 1.04 µg/cm^2/hour, 0.06x10^{-3} cm/hour, and 715x10^{-6} cm^2/hour (Muhammad et al. 2005).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

In humans exposed for 2 hours to a mixture of industrial xylene containing 40.4% ethylbenzene, the estimated solvent retention in adipose tissue was 5% of the total uptake (Engstrom and Bjurstrom 1978). Since there was no indication of differences in turnover rates of chemicals within the mixture, it is likely that the retention of ethylbenzene in adipose tissue was approximately 2% of the total uptake. No studies were located concerning the distribution of ethylbenzene in humans following exposure to ethylbenzene alone. However, studies by Pierce et al. (1996) suggest that *in vitro,* the partitioning of ethylbenzene from air into human adipose tissue is similar to that observed in rats.

Studies conducted in rats and mice have shown that inhaled ethylbenzene accumulates in adipose tissue (Elovaara et al. 1982; Engstrom et al. 1985; Fuciarelli 2000). In rats and mice exposed to 750 ppm ethylbenzene for 6 hours/day, concentrations of ethylbenzene in mesenteric adipose were 20–60 times higher than steady-state blood concentrations, whereas concentration in liver were similar to blood (Fuciarelli 2000). Concentrations of ethylbenzene in perirenal adipose tissue were reported to increase, although not linearly, with increasing concentrations of ethylbenzene (Engstrom et al. 1985) and in a mixture of solvent vapors containing ethylbenzene (Elovaara et al. 1982). The less-than-linear increase of ethylbenzene in adipose tissue with increasing dose was partially attributed to the induction of drug-metabolizing enzymes occurring with increasing exposure concentrations, altered blood flow to adipose tissue, changes in lung excretion, and changes in the distribution of ethylbenzene in different tissues. Ethylbenzene was shown to be efficiently distributed throughout the body in rats following inhalation exposure to radiolabeled ethylbenzene (Chin et al. 1980b). The highest amounts of radioactivity in

tissues 42 hours after exposure to 230 ppm ethylbenzene for 6 hours were found in the carcass, liver, and gastrointestinal tract, with lower amounts detected in the adipose tissue.

3.4.2.2 Oral Exposure

No studies were located regarding distribution of ethylbenzene in humans or animals following oral exposure.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans following dermal exposure to ethylbenzene.

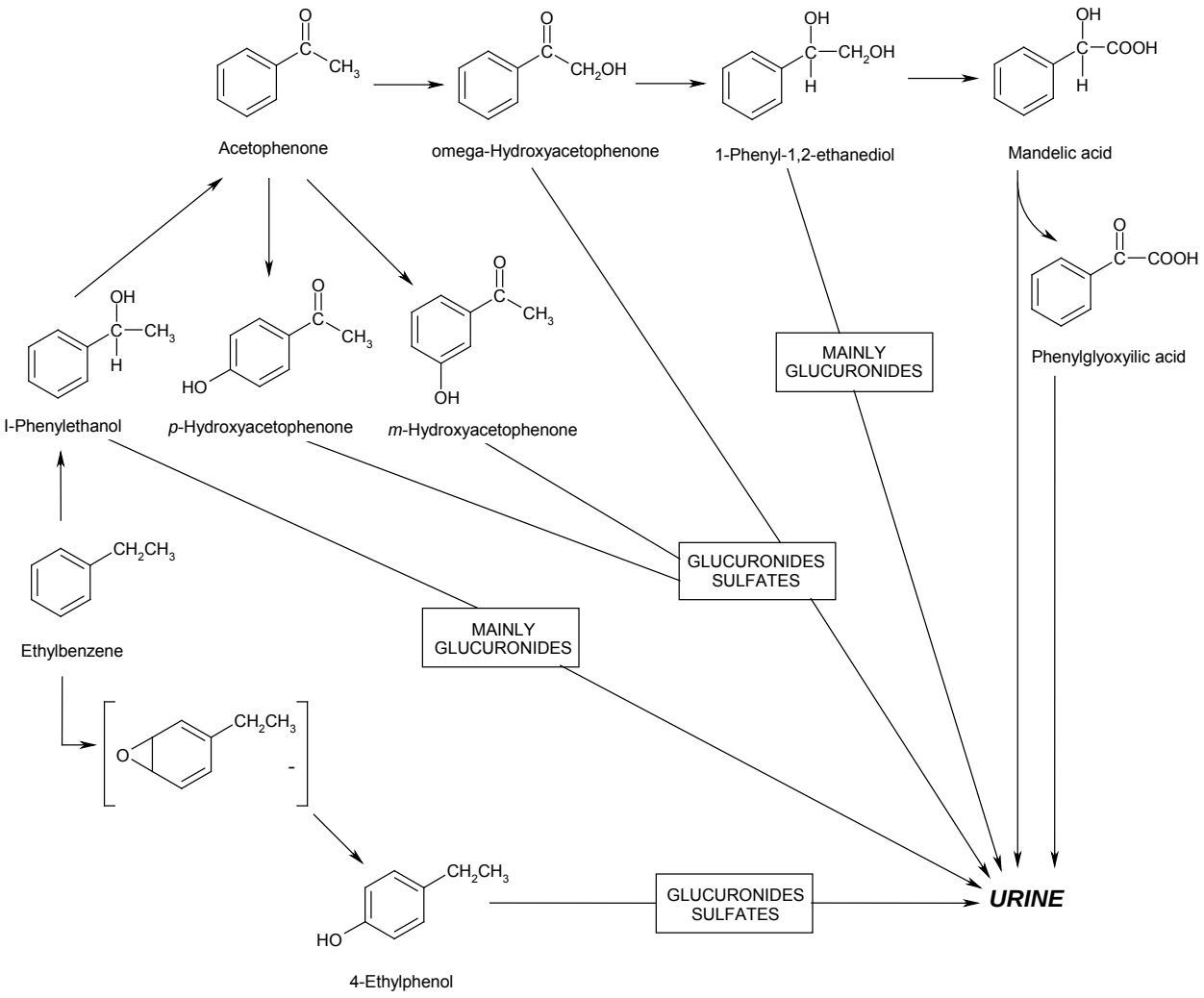
The percentages of absorbed doses following dermal application of [^{14}C]-ethylbenzene in hairless mice were: 15.5%, carcass; 4.5%, application site; 14.3%, expired breath; and 65.5%, excreta (Susten et al. 1990).

3.4.3 Metabolism

The metabolism of ethylbenzene has been studied in humans and other mammalian species. The data demonstrate that ethylbenzene is metabolized mainly through hydroxylation and then through conjugation reactions from which numerous metabolites have been isolated. Figure 3-3 summarizes the proposed metabolic pathway for ethylbenzene in humans (Engstrom et al. 1984). The major urinary metabolites have been identified (Kiese and Lenk 1974; Sullivan et al. 1976). Comparisons of *in vitro* data with data from intact animals indicate that liver microsomal enzymes participate in ethylbenzene hydroxylation (McMahon and Sullivan 1966; McMahon et al. 1969; Sams et al. 2004). In microsomes prepared from human liver, hydroxylation of ethylbenzene to 1-phenylethanol is catalyzed by cytochrome P-450 isoforms CYP2E1 and CYP2B6 (Sams et al. 2004). Adrenal cortex may be a major site of extra-hepatic ethylbenzene metabolism (Greiner et al. 1976). No significant qualitative differences in metabolism between oral and inhalation routes were reported in humans or animals. The metabolism of ethylbenzene has been found to vary with species, sex, and nutritional status. These differences are described below.

In humans exposed via inhalation, the major metabolites of ethylbenzene are mandelic acid (approximately 64–71%) and phenylglyoxylic acid (approximately 19–25%) (Bardodej and Bardodejova 1970; Engstrom et al. 1984; Knecht et al. 2000; Jang et al. 2001; Tardif et al. 1997). Based on data from human, animal, and *in vitro* studies, the metabolic pathway for ethylbenzene in humans was proposed

Figure 3-3. Metabolic Scheme for Ethylbenzene in Humans



Source: Engstrom et al. 1984

(Engstrom et al. 1984). This pathway is shown in Figure 3-3. Evidence indicates that the initial step in this metabolic pathway is oxidation (hydroxylation) of the side chain of ethylbenzene to produce 1-phenylethanol. Microsomal preparations from rat liver have shown that the oxidation of ethylbenzene proceeds with the incorporation of atmospheric oxygen, as opposed to oxygen from water molecules (McMahon et al. 1969). Filipovic et al. (1992) have shown that cytochrome P-$450_{(cam)}$ from *Pseudomonas putida* provides a useful metabolic model for ethylbenzene hydroxylation, converting ethylbenzene to 1-phenylethanol at 98%. 1-Phenylethanol is conjugated to glucuronide, which then is either excreted or converted to subsequent metabolites. Oxidation of 1-phenylethanol yields acetophenone, which is both excreted in the urine as a minor metabolite and further transformed. Continued oxidation of the side chain leads to the sequential formation of 2-hydroxyacetophenone, 1-phenyl-1,2-ethanediol, mandelic acid, and phenylglyoxylic acid. Minor pathways (e.g., ring hydroxylation) include glucuronide and sulfate conjugation with hydroxylated derivatives to form glucuronides and sulfates that are excreted in the urine. Analysis of urine from humans exposed to ethylbenzene via the inhalation route showed that approximately 70 and 25% of the retained dose of ethylbenzene is excreted as mandelic acid and phenylglyoxylic acid, respectively (Bardodej and Bardodejova 1970; Engstrom et al. 1984). Additional metabolites detected in human urine include 1-phenylethanol (4%), *p*-hydroxyacetophenone (2.6%), *m*-hydroxyacetophenone (1.6%), and trace amounts of 1-phenyl-1,2-ethanediol, acetophenone, 2-hydroxyacetophenone, and 4-ethylphenol. Following dermal exposure of humans, however, excretion of mandelic acid was shown to be only 4.6% of the absorbed dose (Dutkiewicz and Tyras 1967), which may indicate differences in the metabolic fate between inhalation and dermal exposure routes. However, the small percentage of absorbed dose accounted for limits the interpretation. No animal data were located which could confirm these metabolic differences following dermal exposure. Generally, ethyl-benzene metabolites and intermediates are thought to be only slightly toxic, since no adverse effects from human experimental exposure have been reported (Bardodej and Bardodejova 1970).

Qualitative and quantitative differences in the biotransformation of ethylbenzene in animals as compared to humans have been reported (Bakke and Scheline 1970; Climie et al. 1983; El Masry et al. 1956; Engstrom et al. 1984, 1985; Smith et al. 1954a, 1954b; Sollenberg et al. 1985). The major metabolites of ethylbenzene differ from species to species, and different percentages of the metabolites are seen in different species. The principal metabolic pathway in rats is believed to begin with oxidation (hydroxylation) of the side chain as in humans (Climie et al. 1983; Engstrom et al. 1984, 1985; Smith et al. 1954a). In rats exposed by inhalation or orally to ethylbenzene, the major metabolites were identified as benzoic acids and glycine conjugates (e.g., hippuric acid; approximately 38%), 1-phenylethanol (approximately 25%), and mandelic acid (approximately 15–23%), with phenylglyoxylic acid making up

only 10% of the metabolites (Climie et al. 1983; Engstrom et al. 1984, 1985; Fuciarelli 2000). The urinary excretion rate of mandelic acid in rats exposed to 250 ppm ethylbenzene, 6 hours/day for 15 days was the same after the first exposure as it was after the last exposure. In contrast, excretion in the 1,000 ppm group was 2–5 times higher after the last exposure than it was after the first exposure (Saillenfait et al. 2006). Both *in vivo* studies using rats and *in vitro* studies using rat liver microsomes showed that 4-ethylphenol was also produced from ethylbenzene, perhaps by rearrangement of corresponding arene oxides (Bakke and Scheline 1970; Kaubisch et al. 1972). Kaubisch et al. (1972) also showed that 2-hydroxyethylbenzene was produced from ethylbenzene *in vitro* in the presence of rat liver microsomes. The level of ethylbenzene exposure was shown to affect the metabolic pattern. This was thought to be due either to selective enzymatic induction in the biotransformation of ethylbenzene or to delayed excretion of certain metabolites with increasing doses.

Acetophenone was detected (quantitative data were not provided) in blood of rats and guinea pigs exposed to ethylbenzene in air at 500 ppm, 8 hours/day for 3 days (Cappaert et al. 2002). Further clarification of ethylbenzene metabolic pathways was provided by Sullivan et al. (1976). Using intraperitoneally dosed rats, the authors demonstrated that the conversion of 1-phenylethanol to mandelic acid initially involves oxidation to acetophenone. Acetophenone was considered to be the precursor of mandelic acid, benzoylformic acid, and benzoic acid. A similar study in which rabbits were intraperitoneally injected with a single dose of 250 mg ethylbenzene/kg body weight was conducted by Kiese and Lenk (1974). This study showed that between 1 and 10% of the dose was excreted as 1-phenylethanol in the urine and <1% was excreted in the urine as 2-hydroxyacetophenone, *p*-hydroxy-acetophenone, and *m*-hydroxyacetophenone.

Rabbits given an oral dose of ethylbenzene showed the major metabolic pathway to be hydroxylation of the α-carbon to 1-phenylethanol, which is oxidized further to a number of intermediates and metabolites (El Masry et al. 1956; Smith et al. 1954a). Many of these intermediates are subsequently conjugated to glucuronides and sulfates and excreted. In rabbits, the most important metabolite is hippuric acid, which is probably formed by oxidative decarboxylation of phenylglyoxylic acid (El Masri et al. 1958). Oxidation of the methyl group of ethylbenzene was also shown to occur, as evidenced by the presence of phenaceturic acid in the urine. A slight increase in the excretion of thioether suggests that glutathione conjugation may also play a minor role.

The nutritional status of animals was demonstrated to have a marked effect on ethylbenzene metabolism in rats (Nakajima and Sato 1979). The *in vitro* metabolic activity of liver microsomal enzymes on ethyl-

benzene was shown to be significantly enhanced in fasted rats despite a marked loss of liver weight. No significant increases in the microsomal protein and cytochrome P-450 contents were detected in fasted rats compared with fed rats. In addition, the metabolic rate in fasted males was significantly higher than in fasted females, but the difference in rates decreased following food deprivation for 3 days. These results suggest possible sex differences in the rate of ethylbenzene metabolism. However, it is not known if such differences exist in the normally fed rats.

Metabolism of ethylbenzene has not been studied in children or immature animals. However, some members of two of the enzyme superfamilies involved in conjugation of phase I ethylbenzene metabolites are known to be developmentally regulated. In humans, UDP glucuronosyltransferase activity does not reach adult levels until about 6–18 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases seems to develop earlier, although again, it is isoform specific. The activity of some sulfotransferase isoforms may even be greater during infancy and early childhood than in adults (Leeder and Kearns 1997).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Excretion of ethylbenzene has been studied in humans and in a number of animal species. Ethylbenzene has been shown to be rapidly metabolized and then eliminated from the body, primarily as urinary metabolites. The major metabolic products have been previously described in Section 3.4.3.

Elimination of ethylbenzene has been studied in volunteers exposed by inhalation (Bardodej and Bardodejova 1970; Dutkiewicz and Tyras 1967; Engstrom and Bjurstrom 1978; Gromiec and Piotrowski 1984; Knecht et al. 2000; Tardif et al. 1997; Yamasaki 1984) and in humans exposed by inhalation in the occupational setting (Holz et al. 1995; Jang et al. 2001; Kawai et al. 1991, 1992; Ogata and Taguchi 1988). Elimination of ethylbenzene in exhaled air in volunteers exposed to 33 ppm ethylbenzene exhibited multi-phasic kinetics with an early-phase half time of <1 hour (Tardif et al. 1997). This elimination rate is similar to the rate of elimination of ethylbenzene from blood following cessation of exposure (Knecht et al. 2000; Tardif et al. 1997) and is considerably faster than the rate of elimination (i.e., urinary excretion) of the metabolites, mandelic acid ($t_{1/2}$≈3–5 hours) and phenylgloxylic acid ($t_{1/2}$≈10–12 hours) (Gromiec and Piotrowski 1984; Knecht et al. 2000; Tardif et al. 1997). Elimination of mandelic acid was reported to be biphasic, with half-lives of 3.1 hours for the rapid phase and 25 hours for the slow phase (Gromiec and Piotrowski 1984). During the 8-hour exposure, 23% of the retained

ethylbenzene was eliminated in the urine, and 14 hours following termination of exposure an additional 44% of the retained ethylbenzene was eliminated. The highest excretion rate of urinary metabolites in humans exposed to ethylbenzene by inhalation occurred 6–10 hours after the beginning of exposure (Gromiec and Piotrowski 1984; Yamasaki 1984).

Concentrations of ethylbenzene metabolites in before-shift and after-shift urine were significantly higher in workers exposed to 85 to >921 ppm ethylbenzene in a styrene plant than in control workers exposed to 33.4–66.8 ppm (Holz et al. 1995).

A statistically significant correlation was observed between urinary excretion of mandelic acid and ethylbenzene exposure in workers exposed to mixed solvents (including an ethylbenzene time-weighted average [TWA] of 0.9 ppm) in a metal-coating factory (Kawai et al. 1991). No correlation was observed between ethylbenzene exposure and phenylglyoxylic acid urinary excretion. In a study of chronic-duration exposure at lower levels (2.1 and 2.3 ppm for geometric and arithmetic mean, respectively), no significant correlation was observed between ethylbenzene exposure and urinary excretion of phenylglyoxylic acid and mandelic acid (Kawai et al. 1992).

In animals, elimination of ^{14}C-ethylbenzene following inhalation exposure is rapid and occurs primarily via urinary excretion (Chin et al. 1980a, 1980b; Engstrom et al. 1984, 1985) and to a much lesser degree via the feces, and expired “gasses” and carbon dioxide (Chin et al. 1980b). Rats exposed to 230 ppm radiolabeled ethylbenzene for 6 hours via inhalation excreted virtually all of the radioactivity within 24 hours after the onset of exposure (Chin et al. 1980a, 1980b). Ninety-one percent of the radioactivity was recovered, primarily in the form of urinary metabolites. In a similar inhalation experiment using rats exposed to 300 or 600 ppm, urinary excretion was reported to be 83 and 59% of the absorbed dose within 48 hours after the onset of exposure, with 13% eliminated during the first 6 hours of exposure (Engstrom et al. 1984).

Quantitative differences between species in the percentages of metabolites excreted in the urine were also reported by Chin et al. (1980a). In this report, urinary metabolites in dogs and rats exposed to ethylbenzene by inhalation were studied. Although similarities in the types of metabolites recovered following inhalation exposure were reported, quantitative differences, albeit minor ones, were noted in the ratio of metabolites present in the urine. These results were attributed to differences in metabolism between dogs and rats.

Elimination of inhaled ethylbenzene from blood, fat, liver, and lung tissue following inhalation exposures is biphasic in rats and mice (Fuciarelli 2000). The terminal phase for blood is approximately 4–7 times slower than the initial phase. For example, in male rats exposed to 75 ppm for 6 hours, the initial and terminal elimination half-times were approximately 77 and 493 minutes, respectively. Blood elimination kinetics of inhaled ethylbenzene are dependent on exposure concentration, with decreasing clearance of ethylbenzene from blood in association with increasing exposure concentration. In female mice, rate constants for ethylbenzene measured at the conclusion of 4-hour exposures to concentrations ranging from 75 to 1,000 ppm were 0.21 $minute^{-1}$ ($t_{1/2}$=3.3 minute) at 75 ppm and 0.011 $minute^{-1}$ ($t_{1/2}$=63 minutes) at 1,000 ppm; similar decreases in elimination rate were observed in male mice (Charest-Tardif et al. 2006). Elimination half-life values increased approximately 2-fold, with the 10-fold increase in exposure concentration, and the ratio of the area under the curve (AUC) for ethylbenzene in blood/exposure concentration increased 10–20-fold (Fucareli 2000). The concentration dependence on elimination is consistent with a capacity limitation in metabolism of ethylbenzene. Elimination rates measured in mice after 1 or 7 days of 4-hour exposures to 75 ppm ethylbenzene were similar; however, elimination rates increased following 7 days of exposure to 750 ppm (e.g., 0.016 $minute^{-1}$, $t_{1/2}$=43.3 minutes, female mice), compared to 1 day of exposure (0.061 $minute^{-1}$, $t_{1/2}$=11.4 minutes, female mice; Charest-Tardif et al. 2006). These observations are consistent with induction of metabolic clearance of ethylbenzene in association with repeated exposures to 750 ppm. Elimination rates of ethylbenzene from blood were faster in mice compared to rats. In rats exposed to 75 ppm ethylbenzene for 6 hours, the rate for the initial phase of elimination was 0.00902 $minute^{-1}$ ($t_{1/2}$=76.8 minutes) in male rats and 0.0102 $minute^{-1}$ ($t_{1/2}$=68.1 minutes) in female rats. In mice the elimination rates were 0.0596 $minute^{-1}$ ($t_{1/2}$=11.6 minutes) in male mice, and 0.109 $minute^{-1}$ ($t_{1/2}$=6.36 minutes) in female mice (Fuciarelli 2000).

3.4.4.2 Oral Exposure

No studies were located regarding the excretion of ethylbenzene metabolites in humans following oral exposure to ethylbenzene.

Elimination of ethylbenzene and its metabolites in animals after oral exposure has been shown to be similar to that following inhalation exposure. Female rats administered a single oral dose of 30 mg radiolabeled ethylbenzene/kg/body weight showed very rapid elimination, mostly in the urine (Climie et al. 1983). Eighty-two percent of the radioactivity was detected in the urine, while 1.5% was detected in the feces. The major metabolites were mandelic acid (23%) and hippuric acid (34%), with 1-phenylethyl glucuronide detected as a minor metabolite. Relatively minor metabolites (e.g., 4-ethylphenol, 2-phenyl-

ethanol, 1-phenylethanol) were shown to be excreted in the urine of male rats exposed to a single oral dose of 100 mg/kg ethylbenzene administered by gavage in oil (Bakke and Scheline 1970). No data on the major metabolites were provided in this study.

In a similar study in which male rats were given single oral doses of 350 mg/kg/body weight ethylbenzene, the excretion of mandelic acid and phenylglyoxylic acid was detected in the first urine sample after exposures. Peak concentration was reached within 17 hours, and ethylbenzene was virtually eliminated 48 hours following the onset of exposure (Sollenberg et al. 1985).

As in inhalation experiments, quantitative and qualitative differences between species were shown to exist in the percentages of metabolites excreted in the urine. Rabbits orally exposed to ethylbenzene excreted large amounts of glucuronide conjugates in the urine (El Masry et al. 1956; Smith et al. 1954a, 1954b) instead of mandelic acid, hippuric acid, and phenylglyoxylic acid, which are the major metabolites in rats (see above). Glucuronide conjugates accounted for 32% of the administered dose, with mandelic acid making up only 2% of the administered dose (El Masry et al. 1956). These results were confirmed in a study by Smith et al. (1954a, 1954b), who detected 32% of a single oral dose of ethylbenzene (433 mg/kg) administered to rabbits as glucuronide conjugates excreted in the urine.

3.4.4.3 Dermal Exposure

In humans, the pattern of excretion of ethylbenzene metabolite following dermal exposure has been shown to differ significantly from the pattern in which humans have been exposed by inhalation. Dermal absorption of ethylbenzene in aqueous solutions was estimated as the difference of the ethylbenzene concentrations in solution before and after exposure. The urinary excretion of mandelic acid in humans dermally exposed to ethylbenzene for 2 hours was only 4.6% of the absorbed ethylbenzene (Dutkiewicz and Tyras 1967). Urine was collected periodically during the 2-hour exposure period and a 10-hour follow-up. Interpretation is difficult due to the small percentage of absorbed dose accounted for. No ethylbenzene was reported to be excreted in exhaled air. No further details on the excretion patterns were provided.

Susten et al. (1990) conducted *in vivo* percutaneous absorption studies of ethylbenzene in Hairless mice. Results showed total absorption (sums of radioactivity found in the excreta, carcass, skin application site, and expired breath) was 3.4% of the nominal dose. The absorbed dose collected in expired breath during the first 15 minutes of ethylbenzene application was 9.3%. The percentage of absorbed doses following

dermal application of [^{14}C]-ethylbenzene are as follows: 15.5% in the carcass; 4.5% at the application site; 14.3% in expired breath; and 65.5% in excreta.

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

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

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

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

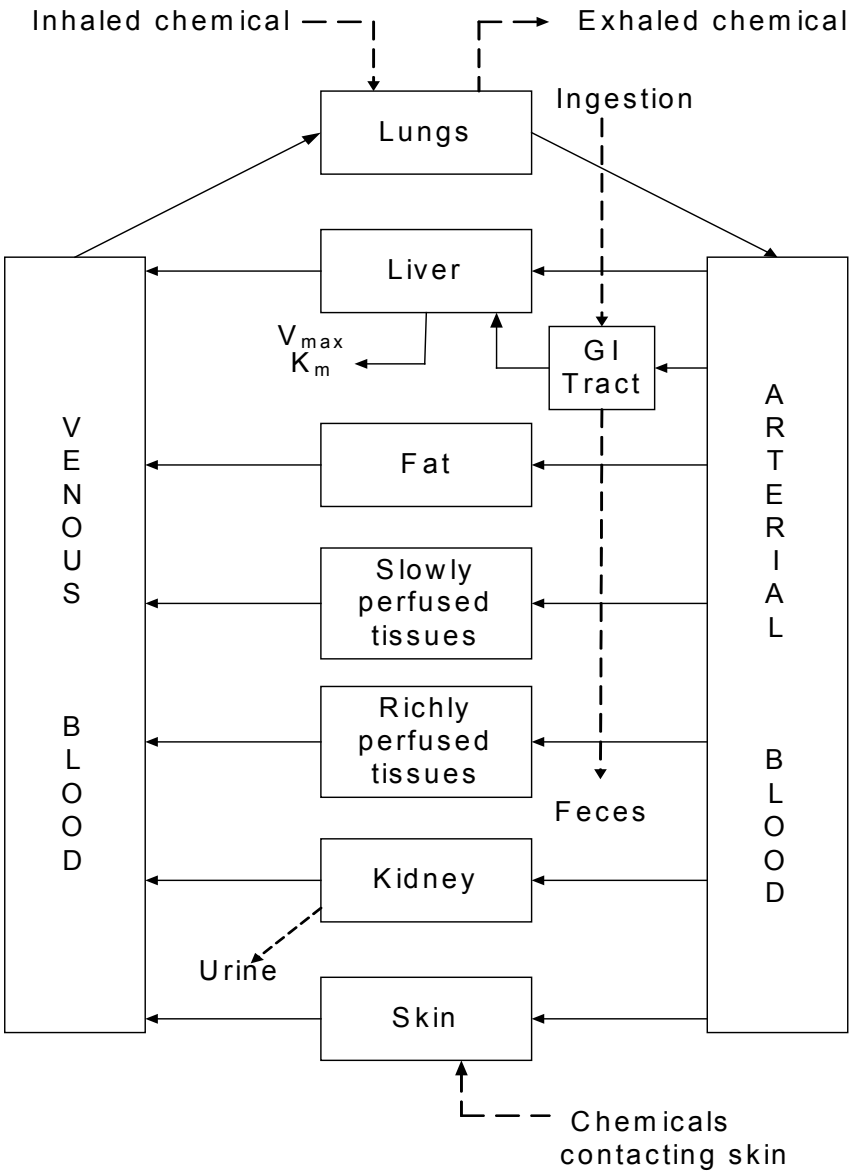
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many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

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

If PBPK models for ethylbenzene 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 models have been developed that simulate the kinetics of inhaled ethylbenzene in animals and humans (Dennison et al. 2003; Haddad et al. 1999, 2000, 2001; Jang et al 2001; Nong et al. 2007; Tardif et al. 1997). The Dennison et al. (2003) and Tardif et al. (1997) inhalation models have been incorporated into models of gasoline component mixture models (Dennison et al. 2004, 2005; Haddad et al. 2001). An extension of the Tardif et al. (1997) model has been reported that includes simulation of gastrointestinal absorption (i.e., transfer of ingested ethylbenzene to liver) of ethylbenzene in rats (Faber et al. 2006). A model of dermal absorption ethylbenzene in human has also been reported (Shatkin and Brown 1991). Models that simulate kinetics of ingested ethylbenzene have not been reported. In general, all of the inhalation models of have similar structures, with the major conceptual differences being the simulation of metabolism and excretion of metabolites. The Nong et al. (2007) mouse model simulates metabolism of ethylbenzene in liver, lung, and richly perfused tissues, whereas all other models attribute all ethylbenzene metabolism to the liver. The Nong et al. (2007) mouse model also simulated changes in ethylbenzene blood kinetics in mice that occurred with repeated exposure to ethylbenzene at exposure concentrations >75 ppm. These changes were attributed to induction of cytochrome P450 and were simulated as an increase in V_{max} for metabolism of ethylbenzene in liver. The Jang et al. (2001) human model simulates excretion of the ethylbenzene metabolite, mandelic acid, whereas other models do not

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

simulate the urinary elimination pathway. The Tardif et al. (1997), Dennison et al. (2003), and Nong et al. (2007) models are described in greater detail in the sections that follow. Complete documentation of the Jang et al. (2001) model was not available for providing a detailed description of the model, although it appears to be conceptually similar to the Tardif et al (1997) and Dennison et al. (2003) models.

The Tardif et al. (1997; Haddad et al. 1999, 2000, 2001) Model

Description of the Model. Tardif et al. (1997) developed a PBPK model for simulating the kinetics of ethylbenzene, toluene, and xylene in blood following inhalation exposures to the individual chemicals or the ternary mixture (in rats and humans). The structure of the model is essentially identical the generic model depicted in Figure 3-4, with tissue compartments limited to lungs, liver, fat, richly perfused tissues (RPT), and poorly perfused tissues (SPT). All metabolism was attributed to the liver and represented as functions of the concentration of parent compound in liver venous blood, affinity constant (K_m), and maximum reaction velocity (V_{max}). Transfers of parent compound between blood and tissues were assumed to be flow-limited, with clearance represented by tissue blood flow (L/hour). Parameters for the ethylbenzene model are presented in Table 3-6. Tissue: air partition coefficients for ethylbenzene were derived from vial equilibrium studies of isolated rat tissues. Tissue:blood partition coefficients were derived from measured tissue:air and blood:air partition coefficients (i.e., tissue:blood=tissue:air/ blood:air; Tardif et al. 1997). Metabolism parameter values for ethylbenzene were derived by fitting the model to observations of blood ethylbenzene kinetics measured in rats during and following 4-hour exposures to ethylbenzene in a dynamic exposure chamber (Tardif et al. 1996). Physiological parameters, cardiac output (QC), alveolar ventilation rate (QP), and metabolism V_{max} were allometrically scaled across species (i.e., rat to human) as a function of body weight (BW, scaling factor=$BW^{0.75}$). A blood:air partition coefficient for humans was estimated from vial equilibrium measurements made on isolated human blood; human tissue:blood partition coefficients were derived based on tissue:air coefficients for the rat (Tardif et al. 1997).

Subsequent enhancements of the Tardif et al. (1997) model included simulation of kinetics of an inhaled quaternary mixture that included benzene, ethylbenzene, toluene, and xylene (Haddad et al. 1999) or mixtures of the latter quaternary mixture with dichloromethane (Haddad et al. 2000, 2001). In the development of the quaternary mixture model, values for V_{max} and K_m for ethylbenzene were re-estimated by fitting data on kinetics of ethylbenzene in venous blood following 4-hour exposures to ethylbenzene (50, 100, or 200 ppm; Haddad et al. 1999; Tardif et al. 1997). The resulting estimates were similar to the original estimates reported in Tardif et al. (1997): V_{max}=6.39 mg/hour-kg) and K_m=1.04 mg/L.

Table 3-6. Parameter Values for Tardif et al. (1997) Ethylbenzene PBPK Models

Parameter	Definition	Rat model	Human model
Physiological parameters			
VLC	Liver volume (fraction of body)	0.049	0.026
VFC	Fat volume (fraction of body)	0.09	0.19
VSC	Slowly-perfused tissue volume (fraction of body)	0.72	0.62
VRC	Richly-perfused tissue volume (fraction of body)	0.05	0.05
QCC	Cardiac output (L/hour-kg BW)	15[a]	18[a]
QPC	Alveolar ventilation rate (L/hour-kg body weight)	15[a]	18[a]
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.26
QFC	Fat blood flow (fraction of cardiac output)	0.09	0.05
QSC	Slowly-perfused blood flow (fraction of cardiac output)	0.15	0.25
QRC	Richly-perfused blood flow (fraction of cardiac output)	0.51	0.44
Chemical parameters			
PB	Blood:air partition coefficient	42.7	28.0
PL	Liver:blood partition coefficient	1.96[b] (83.8)	2.99[b]
PF	Fat:blood partition coefficient	36.44[b] (1,556)	55.57[b]
PS	Slowly-perfused partition coefficient	0.61[b] (26.0)	0.93[b]
PR	Richly-perfused partition coefficient	1.41[b] (60.3)	2.15[b]
$V_{max}C$	Maximum rate of metabolism (mg/hour-kg body weight)	7.3[a,c]	7.3[a,c]
K_mC	Michaelis-Menten coefficient for metabolism (mg/L)	1.39[c]	1.39[c]

[a]Scaled to body weight ($BW^{0.75}$)
[b]Tissue:blood partition coefficients calculated based on reported, experimentally determined (vial equilibrium), tissue:air partition coefficients for rats (values in parentheses) and blood:air coefficient (PB) measured in rat or human blood; tissue:blood=tissue:air/blood:air.
[c]Values derived by optimization to data on blood ethylbenzene concentrations in rats exposed to ethylbenzene (dynamic chamber).

Although the Tardiff et al. (1997) model was developed to simulate kinetics of inhaled ethylbenzene, Faber et al. (2006) reported an extension of the model that includes simulation of gastrointestinal absorption (i.e., transfer of ingested ethylbenzene to liver) of ethylbenzene in rats. The gastrointestinal absorption rate constant of 0.18 $hour^{-1}$ was estimated by iteratively adjusting the ate constant to achieve agreement with observed blood ethylbenzene kinetics in following a gavage dose of ethylbenzene (180 mg/kg), in corn oil, administered to adult female rats.

Validation of the Model. Optimization of the metabolism parameters against observed blood kinetics of ethylbenzene in rats exposed for 4 hours to 100 or 200 ppm ethylbenzene achieved predicted blood concentration of ethylbenzene that were within 1–2 standard deviations (SD) of the observations. Most of the validation efforts reported in Tardif et al. (1997) were directed at exploring how well the mixture model predicted observed blood kinetics of ethylbenzene, toluene, or xylene in rats during and following exposures to binary or ternary mixtures of the chemicals. Interactions were simulated as competitive, noncompetitive, or uncompetitive inhibition of metabolism, with the values of the inhibition constants derived by fitting the model to observed blood kinetics during and following exposures to binary mixtures. Although the mixture model achieved predictions similar to observations (i.e., within 1–2 SD of observations), this outcome would have been highly influenced by the parameter values selected for each of the individual chemicals, including fitted interaction constants. A more direct evaluation of the ethylbenzene model was explored by comparing predictions of the human model (allometrically scaled from the rat) to ethylbenzene concentrations in blood and in exhaled air observed in human subjects who were exposed to ethylbenzene (33 ppm) for 7 hours/day on 4 different days (Tardif et al. 1991, 1997). Predicted blood and exhaled air concentrations of ethylbenzene (at steady-state and following cessation of exposure) in subjects exposed to ethylbenzene were within 1–2 SD of observations. The Tardif et al. (1997) model has been incorporated into a mixtures model of JP-8 vapor and its components (Campbell and Fisher 2007). The model included simulations of the kinetics of m-xylene and ethylbenzene, with other aromatic components of JP-8 vapor represented as a lumped component. Interactions between *m*-xylene and ethylbenzene were simulated as competitive inhibition of metabolism. The mixtures model predicted kinetics liver concentrations of ethylbenzene in rats during and following 4-hour exposures to JP-8 vapor (380–2,700 mg/m^3) that were similar to observed kinetics (i.e., predicted liver concentrations were within 1–2 SD of observations).

Risk Assessment. The ethylbenzene model predicts blood kinetics of ethylbenzene and kinetics of metabolism of ethylbenzene that occur in association with inhalation exposures. These predictions are

potentially useful for predicting inhalation-derived internal doses of ethylbenzene in rats and/or humans (e.g., blood concentrations, liver concentrations of parent compound, or amounts of total metabolites formed in the liver), and for making extrapolations of these internal dose metrics across species. The applicability any of the above dose metrics to risk assessment will depend on the mechanism for the specific toxicity end point being assessed, and contribution of the parent compound and/or metabolism metabolites to toxicity (see Section 3.5.2, Mechanisms of Toxicity).

The Tardif et al. (1997) ethylbenzene model has been incorporated into a mixtures model for alkylbenzenes (ethylbenzene, toluene, *m*-xylene), benzene, and dichloromethane (DCM), (Haddad et al. 2001). This mixture model has been applied to the derivation of interaction coefficients for various endpoints of dichloromethane toxicity (i.e., hypoxia, central nervous system effects, and cancer) based on predictions of corresponding relevant DCM internal dose metrics (i.e., carboxyhemoglobin concentration, area under concentration-time curve for DCM in richly perfused tissues; time-integrated amount of DCM conjugated with GSH). Interactions were simulated as dose addition, with internal dose metrics representing dose and the sole interaction mechanism assumed to be competitive inhibition of cytochrome P-450-mediated metabolism of DCM. The Tardif et al. (1997) model also has been incorporated into a mixtures model of JP-8 vapor and its components (Campbell and Fisher 2007). The model included simulations of the kinetics of *m*-xylene and ethylbenzene, with other aromatic components of JP-8 vapor represented as a lumped component. Interactions between *m*-xylene and ethylbenzene were simulated as competitive inhibition of metabolism. The Tardif et al. (1997) mixtures model was also utilized to evaluate occupational exposure limits for ethylbenzene, toluene, *m*-xylene for hypothetical exposures to ternary mixtures of the chemicals (Dennison et al. 2005). These analyses demonstrate the potential utility of the ethylbenzene model for predicting metabolic interactions with other chemicals that share a common mechanism of metabolic elimination, and the potential impacts of such interactions on risk (e.g., hazard index, cancer risk, occupation exposure limits).

Target Tissues. The Tardif et al. (1997) ethylbenzene model was calibrated and evaluated to predict blood kinetics of ethylbenzene that occur in association with inhalation exposures. Essential to this prediction is the accurate prediction of rates of metabolism of ethylbenzene, which, in the model, is attributed solely to the liver. The model has potential utility for predicting, in addition to blood kinetics of ethylbenzene, kinetics of concentrations of ethylbenzene in important toxicity target tissues, including liver and richly perfused tissues (which includes kidney and central nervous system), and rates of metabolism of ethylbenzene and total amount of metabolites formed in liver. The model does not simulate, specifically, the kidney or central nervous system.

Species Extrapolation. The Tardif et al. (1997) model was initially developed and calibrated to simulate kinetics of inhaled ethylbenzene in the rat, and was allometrically scaled to the human. The scaled human model was evaluated for predicting ethylbenzene blood concentrations observed in human subjects who were exposed to ethylbenzene (33 ppm) for 7 hours/day on 4 different days (Tardif et al. 1991). Predicted blood concentrations of ethylbenzene in subjects exposed to ethylbenzene were within 1–2 SD of observations. Studies of the robustness of the model for predicting ethylbenzene kinetics in other species (after allometric scaling to those species) were not located.

Interroute Extrapolation. The Tardiff et al. (1997) model was developed to simulate kinetics of inhaled ethylbenzene in rats and humans. An extension of the model that includes a gastrointestinal absorption rate constant enables simulation of gavage dosing in rats administered ethylbenzene in corn oil (Faber et al. 2006). The gastrointestinal model has not been evaluated for applications to human oral exposures. Studies that evaluated the model for predicting ethylbenzene kinetics following dermal exposure were not located.

The Nong et al. (2007) Model

Description of the Model. Nong et al. (2007) developed a PBPK model for simulating the kinetics of inhalation exposures of ethylbenzene in mice. The structure of the model is essentially identical to the Tardif et al. (1997) model (Figure 3-4, with tissue compartments limited to lungs, liver, fat, richly perfused tissues, and poorly perfused tissues), with the addition of metabolism of ethylbenzene in richly and poorly perfused tissues (K_m, V_{max}). Parameter values are presented in Table 3-7. Values for V_{max} in naive (not induced) liver were derived my allometric scaling ($BW^{0.75}$) of values estimated for the rat and values for K_m in liver were assumed to be the same as in the rat (Haddad et al. 2000). The value for V_{max} was subsequently optimized against data on venous blood kinetics in mice exposed to ethylbenzene concentrations ranging from 75 to 1,000 ppm (Nong et al. 2007). The model overpredicted observations in animals exposed to 750 ppm; adequate fit was achieved by upward adjustment of the V_{max} by a factor of 3. This adjustment achieved adequate fit to blood kinetics observed in animal repeatedly exposed (12 days) to 75 or 750 ppm and was adopted to account for induction of cytochrome P450 in animals exposed repeatedly to ethylbenzene at concentrations >75 ppm (Nong et al. 2007). The value for V_{max} in lung was derived from estimates made in *in vitro* preparation of mouse lung microsomes (Nong et al. 2007) and was scaled to lung weight. Values for K_m in lung and V_{max} and K_m in richly perfused tissues were derived by optimization against data on venous blood kinetics in mice exposed to ethylbenzene

Table 3-7. Parameter Values for Nong et al. (2007) Ethylbenzene Mouse Physiologically-based Pharmacokinetic Model

Parameter	Definition	Male	Female
Physiological parameters			
VLC	Liver volume (fraction of body)	0.06	0.06
VLUC	Lung volume (fraction of body)	0.0073	0.0073
VFC	Fat volume (fraction of body)	0.1	0.1
VSC	Slowly-perfused tissue volume (fraction of body)	0.70	0.70
VRC	Richly-perfused tissue volume (fraction of body)	0.05	0.05
QCC	Cardiac output (L/hour-kg BW)	24[a]	24[a]
QPC	Alveolar ventilation rate (L/hour-kg body weight)	16[a]	16[a]
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.25
QLUC	Lung blood flow (fraction of cardiac output)	1.00	1.00
QFC	Fat blood flow (fraction of cardiac output)	0.09	0.09
QSC	Slowly-perfused blood flow (fraction of cardiac output)	0.15	0.15
QRC	Richly-perfused blood flow (fraction of cardiac output)	0.51	0.51
Chemical parameters			
PB	Blood:air partition coefficient	42.8	65.4
PL	Liver:blood partition coefficient	1.38[b] (72.9)	1.12[b] (72.9)
PLU	Lung:blood partition coefficient	1.21[b] (63.8)	0.98[b] (63.8)
PF	Fat:blood partition coefficient	26.84[b] (1417)	21.67[b] (1417)
PS	Slowly-perfused partition coefficient	0.86[b] (45.6)	0.70[b] (45.6)
PR	Richly-perfused partition coefficient	1.38[b,c] (72.9)	1.12[b,c] (72.9)
V_{max}CL	Maximum rate of metabolism in liver for exposures ≤75 ppm (mg/hour-kg body weight)	7.3[d]	7.3[d]
K_mCL	Michaelis-Menten coefficient for metabolism in liver (mg/L)	1.04	1.04
V_{max}CL	Maximum rate of metabolism in liver for repeated exposures >75 ppm (mg/hour-kg body weight)	19.2[d]	19.2[d]
K_mCL	Michaelis-Menten coefficient for metabolism in liver (mg/L)	1.04	1.04
V_{max}CLU	Maximum rate of metabolism in lung (mg/hour-kg body weight)	13.4[d]	13.4[d]
K_mCLU	Michaelis-Menten coefficient for metabolism in lung (mg/L)	5.57	4.35

Table 3-7. Parameter Values for Nong et al. (2007) Ethylbenzene Mouse Physiologically-based Pharmacokinetic Model

Parameter	Definition	Male	Female
V_{max}CRP	Maximum rate of metabolism in rapidly perfused tissue (mg/hour-kg body weight)	17.4[d]	12.9[d]
K_mCRP	Michaelis-Menten coefficient for metabolism in rapidly perfused tissue (mg/L)	2.33	1.15

[a]Scaled to body weight ($BW^{0.75}$).
[b]Tissue:blood partition coefficients calculated based on reported, experimentally determined (vial equilibrium), tissue:air partition coefficients for rats (values in parentheses) and blood:air coefficient (PB) measured in rat or human blood; tissue:blood=tissue:air/blood:air.
[c]Values shown are for liver; values reported for tissue:air were as follows: brain, 51.44; heart, 61.16; and kidney, 68.53 corresponding values for tissue:blood were: brain, 0.97 (male), 0.79, female); heart, 1.16 (male), 0.94 (female); and kidney, 1.30 (male), 1.05 (female).
[d]Scaled to body weight ($BW^{0.74}$).

concentrations ranging from 75 to 1,000 ppm (Nong et al. 2007). Tissue:air partition coefficients for ethylbenzene were derived from vial equilibrium studies of isolated tissues, and included blood:air coefficients determined in male (52.8±3 standard error [SE]) and female (65.4±5 SE) mice. Tissue:blood partition coefficients for male and female mice were derived from measured gender-specific blood:air partition coefficients and tissue:air coefficitent (i.e., tissue:blood=tissue:air/blood:air). Physiological parameters, cardiac output (QC) and alveolar ventilation rate (QP), and metabolism V_{max} were allometrically scaled as a function of body weight.

Validation of the Model. Metabolism parameters were optimized against observed blood kinetics of ethylbenzene in mice exposed for 4 hours to 75 or 1,000 ppm ethylbenzene. The optimized model was evaluated against observations of blood, liver, lung, and fat concentrations of ethylbenzene in male or female mice repeatedly exposed to 750 ppm ethylbenzene (12 days, 6 hours/day) and predictions were within 1–2 SDs of the observations.

Risk Assessment. The Nong et al. (2007) model predicts blood kinetics of ethylbenzene and kinetics of metabolism of ethylbenzene that occur in association with inhalation exposures. These predictions are potentially useful for predicting inhalation-derived internal doses of ethylbenzene in mice and/or humans (e.g., blood concentrations, liver concentrations of parent compound, or amounts of total metabolites formed in the liver), and for making extrapolations of these internal dose metrics across species. However, a human model that includes simulation of metabolism of ethylbenzene in lung and rapidly perfused tissue has not been reported. The applicability any of the above dose metrics to risk assessment will depend on the mechanism for the specific toxicity end point being assessed, and contribution of the parent compound and/or metabolism metabolites to toxicity (see Section 3.5.2, Mechanisms of Toxicity).

Target Tissues. The Nong et al. (2007) ethylbenzene model was calibrated and evaluated to predict blood, liver, lung, and fat kinetics of ethylbenzene that occur in association with inhalation exposures to mice. The model has potential utility for predicting, in addition to blood kinetics of ethylbenzene, kinetics of concentrations of ethylbenzene in important toxicity target tissues, including liver and richly perfused tissues (which includes kidney and central nervous system), and rates of metabolism of ethylbenzene and total amount of metabolites formed in liver, lung, and other rapidly perfused tissues (e.g., brain, heart, kidney). The model does not simulate, specifically, the kidney or central nervous system.

Species Extrapolation. The Nong et al. (2007) model was initially developed and calibrated to simulate ethylbenzene kinetics in the mouse. The model could be allometrically scaled to other species (e.g., humans). Studies of the robustness of the model for predicting ethylbenzene kinetics in other species (after allometric scaling to those species) were not located.

Interroute Extrapolation. The Nong et al. (2007) model was developed to simulate kinetics of inhaled ethylbenzene. Studies that evaluated the model for predicting ethylbenzene kinetics following oral or dermal exposure were not located.

The Dennison et al. (2003, 2004) Model

Description of the Model. Dennison et al. (2003, 2004) developed a PBPK model for simulating the blood and elimination kinetics of components of gasoline, including benzene, ethylbenzene, *n*-hexane, toluene, *o*-xylene, and other volatile components (represented as a single lumped composition) in rats. The structure of the model is essentially identical the generic model depicted in Figure 3-4, with tissue compartments limited to lungs, liver, fat, richly perfused tissues (RPT), and slowly perfused tissues (SPT). All metabolism was attributed to the liver and represented as functions of the concentration of parent compound in liver venous blood, affinity constant (K_m), and maximum reaction velocity (V_{max}). Transfers of parent compound between blood and tissues were assumed to be flow-limited, with clearance represented by tissue blood flow (L/hour). Parameters for the ethylbenzene portion of the model are presented in Table 3-8. Partition coefficients for ethylbenzene were derived from vial equilibrium studies of isolated rat tissues (Tardif et al. 1997). Metabolism parameter values for ethylbenzene were derived by fitting the model to observations of blood ethylbenzene kinetics measured in rats during closed-chamber exposure to ethylbenzene (approximately 2,000 ppm starting chamber concentration; Dennison et al. 2003). Physiological parameters, cardiac output (QC), and alveolar ventilation rate (QP), and metabolism V_{max} were allometrically scaled to body weight (BW, scaling factor=$BW^{0.74}$)

Validation of the Model. Optimization of the metabolism parameters for rats against observed closed chamber air concentration kinetics achieved predicted elimination kinetics of ethylbenzene that were similar to observations (Dennison et al. 2003). Validation efforts reported in Dennison et al. (2004) were directed at exploring how well the mixture model predicted observed closed chamber air kinetics of ethylbenzene, toluene, or xylene during exposures of rats to gasoline (1, 10, 100, 1,000 ppm). Interactions were simulated as competitive inhibition of metabolism, with the values of the inhibition constants derived by fitting to chamber air concentration kinetics during exposures to binary mixtures.

Table 3-8. Parameter Values for Dennison et al. (2003) Ethylbenzene PBPK Model

Parameter	Definition	Rat model
Physiological parameters		
VLC	Liver volume (fraction of body)	0.037
VFC	Fat volume (fraction of body, scaled to body weight)	0.036(body weight)+0.205
VSC	Slowly-perfused tissue volume (fraction of body)	0.91-remaining[a]
VRC	Richly-perfused tissue volume (fraction of body)	0.054
VLBV	Lung blood volume (fraction of body)	0.002
QCC	Cardiac output (L/hour-kg body weight)	15[b]
QPC	Alveolar ventilation rate (L/hour-kg body weight)	15[b,c]
QLC	Liver blood flow (fraction of cardiac output)	0.183
QSC	Fat blood flow (fraction of cardiac output)	0.07
QFC	Slowly-perfused blood flow (fraction of cardiac output)	0.237[d]
QRC	Richly-perfused blood flow (fraction of cardiac output)	0.51
Chemical parameters		
PB	Blood:air partition coefficient	42.7[e]
PL	Liver:blood partition coefficient	1.96[e]
PF	Fat:blood partition coefficient	36.4[e]
PS	Slowly-perfused partition coefficient	0.609[e]
PR	Readily-perfused partition coefficient	1.96
$V_{max}C$	Maximum rate of metabolism (mg/hour-kg body weight)	7.6[b,f]
K_mC	Michaelis-Menten coefficient for metabolism (mg/L)	0.10[f]

[a]VSC=0.91-(VLC+VFC+VRC+VLB)
[b]Scaled to body weight ($BW^{0.74}$)
[c]QPC varied with exposure: 14.9 at 500 ppm, 13.1 at 1,000 ppm, and 12.5 at 1,500 ppm.
[d]QSC=1-(QLC+QFC+QRC)
[e]Tissue:blood partition coefficients calculated based on reported, experimentally determined (vial equilibrium) tissue:air partition coefficients for rats (Tardif et al. 1997).
[f]Values derived by optimization to data on blood ethylbenzene concentrations in rats exposed to ethylbenzene (closed chamber).

Although the mixture model achieved predictions similar to observations, this outcome would have been highly influenced by the parameter values selected for each of the individual chemicals (or lumped chemicals), including fitted interaction constants and, therefore, does not directly address the validity of the ethylbenzene model.

Risk Assessment. The Dennison et al. (2003) ethylbenzene model predicts blood kinetics of ethylbenzene and kinetics of metabolism of inhaled ethylbenzene. These predictions are potentially useful for predicting internal doses of inhaled ethylbenzene in rats (e.g., blood concentrations, liver concentrations of parent compound, or amounts of total metabolites formed in the liver). The applicability any of the above dose metrics to risk assessment will depend on the mechanism for the specific toxicity endpoint being assessed, and contribution of the parent compound and/or metabolism to toxicity. Current knowledge of the mechanism of toxicity of ethylbenzene does not include an understanding of the relative contributions of parent compound or metabolites as proximate toxic agents in the major end points of ethylbenzene toxicity (i.e., kidney, liver, otic, cancer).

The Dennison et al. (2003) ethylbenzene model has been incorporated into a mixtures model for gasoline (benzene, ethylbenzene, *n*-hexane, toluene, *o*-xylene, and other volatile components). In the mixtures model, chemical interactions were attributed to competitive inhibition of metabolism and inhibition constants were derived by fitting model predictions of closed chamber air concentration kinetics during exposures to binary mixtures. The model was used to predict the effect of increasing exposure concentration to gasoline on blood concentrations and amounts of individual mixture components metabolized (Dennison et al. 2004).

Target Tissues. The Dennison et al. (2003) ethylbenzene model was calibrated and evaluated to predict elimination (i.e., metabolism) kinetics of ethylbenzene that occur in association with inhalation exposures. Essential to this prediction is the accurate prediction of rates of metabolism of ethylbenzene, which, in the model, is attributed solely to the liver. The model has potential utility for predicting, in addition to elimination kinetics of ethylbenzene, kinetics of concentrations of ethylbenzene in important toxicity target tissues, including liver, richly perfused tissues (which includes kidney and central nervous system), and rates of metabolism of ethylbenzene and total amount of metabolites formed in liver. The model does not simulate, specifically, the kidney or central nervous system.

Species Extrapolation. The Dennison et al. (2003) ethylbenzene model was developed and calibrated to simulate ethylbenzene kinetics in the rat; however, it could be allometrically scaled to the

human. Studies of the robustness of the model for predicting ethylbenzene kinetics in species other than the rat (after allometric scaling to those species) were not located.

Interroute Extrapolation. Studies that evaluated the model for predicting ethylbenzene kinetics following oral or dermal exposure were not located.

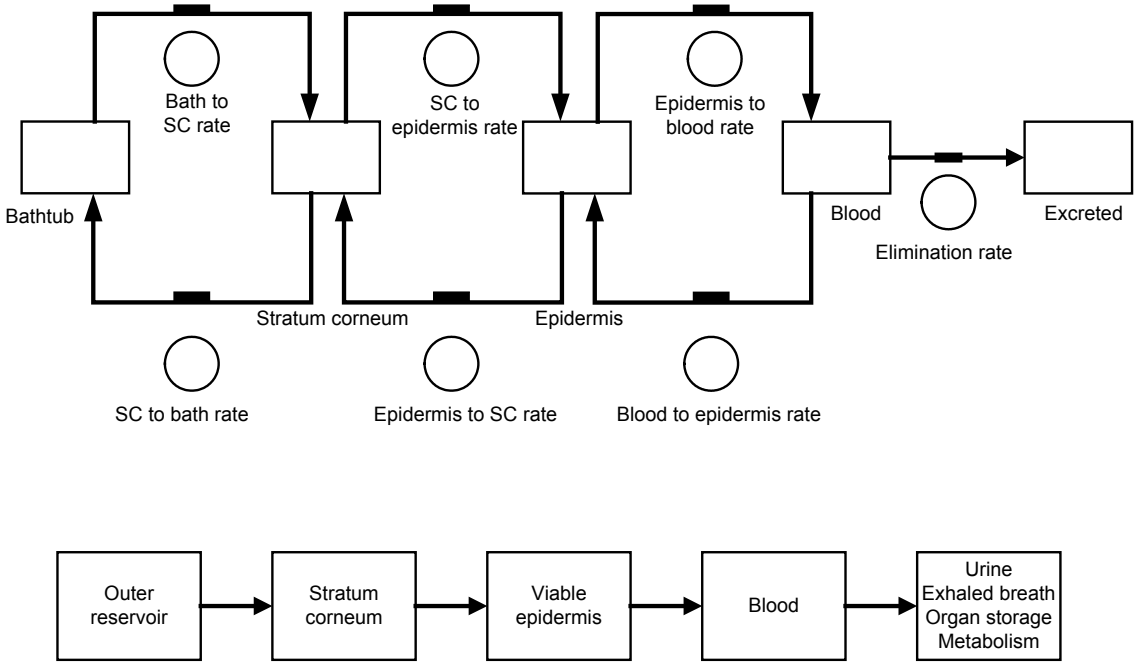
The Shatkin and Brown (1991) Model

Description of the Model. Shatkin and Brown (1991) described a model of dermal absorption of several nonpolar organic nonelectrolytes in dilute aqueous solution, one of which was ethylbenzene. The structure of the model is depicted in Figure 3-5; model parameters are presented in Table 3-9. The model includes three compartments: stratum corneum, viable epidermis, and blood. Transfers of ethylbenzene in solution through the fully hydrated stratum corneum and viable epidermis are assumed to be diffusive, with passage through the stratum corneum being the rate-limiting step. A uniform thickness of 40 μm was assumed for the stratum corneum, with adjustments for different body parts. Immersion of the hand or of the full body was assumed for the predicted models. The viable epidermis was assumed to be 200 μm, although the thickness was varied to test the outcome of the model. Transfer from the viable epidermis to blood was assumed to be flow-limited. Elimination from blood (i.e., distribution to tissues, excretion to urine and air, and metabolism) was represented with a single first-order rate constant. A sensitivity analysis revealed a relatively high influence of epidermal blood flow (as expected for flow-limited transfer to blood), epidermal thickness (increasing thickness decreased absorption), and stratum corneum fat (increasing fat content decreased absorption).

Validation of the Model. Model predictions were compared to the estimates of dermal absorption of ethylbenzene in humans (Dutkiewicz and Tyras 1967, 1968). In this study, adult males (n=7) immersed their hands into a bath solution of 151 mg/L ethylbenzene for 1 hour and the absorbed dose was estimated from the change in concentration of the exposure bath. The model predicted absorption of 34–37% of the bath ethylbenzene in 1 hour, compared to the observed mean absorption of 39% (range, 0.33–0.54). The simulated kinetics of absorption were not reported or compared to observations.

Risk Assessment. The Shatkin and Brown (1991) model is potentially useful for predicting dermal absorption of ethylbenzene in risk assessment applications. An example of one application is prediction of the dermal-absorbed dose of ethylbenzene for a bathing scenario (20-minute immersion in 0.1 mg ethylbenzene/L); the predicted absorbed dose, 0.47–0.50 mg, was higher than the absorbed dose predicted

Figure 3-5. Schematic Representation of the Model of Dermal Absorption



Source: Shatkin and Brown 1991

Table 3-9. Parameters Used in the Shatkin and Brown PBPK Model of Dermal Absorption of Ethylbenzene

Parameter[a]	Value	Reference
Stratum corneum/water partition coefficient (K_m)	NG	Calculated from Roberts et al. 1975
Stratum corneum diffusion coefficient (D_{sc})	NG	Calculated from Guy and Maibach 1984
Skin surface	320 cm^2 (adult, hands and forearms)	Dutkiewicz and Tyras 1967, 1968
	NG (adult, body)	Guy and Maibach 1984
Skin surface (infant)	1,900 cm^2	Guy and Maibach 1984
Epidermis diffusion coefficient (D_e)	$3.6x10^{-4}$ cm^2/minute	Scheuplein 1976; Scheuplein et al. 1969
Stratum corneum thickness (H_{sc})	0.004 cm	Blank and Scheuplein 1969
Epidermis thickness (H_e)	0.02–0.1 cm	Blank and McAuliffe 1985; Blank and Scheuplein 1969; Guy et al. 1982
Epidermal blood flow (F_{eb}) (adult, at rest)	280 mL/minute–m^2	Wade et al. 1962
Epidermal blood flow (F_{eb}) (adult, heavy exercise)	4,000 mL/minute–m^2	Rowell 1986
Epidermis/blood partition coefficient (K_{eb})	2.75	Shatkin and Brown 1991
Stratum corneum/epidermis partition coefficient ($K_{sc/e}$)	NG	Shatkin and Brown 1991
Blood volume (V_b) (adults)	5,000 mL	Shatkin and Brown 1991
Blood volume (V_b) (infants)	693 mL	Shatkin and Brown 1991
Fat in blood	0.7–0.9%	Brown and Hattis 1989
Fat in stratum corneum	3–6%	Raykar et al. 1988
Fat in epidermis	2–2.5%	Scheuplein 1976
Elimination rate constant (K_e)	0.1 $minute^{-1}$	Hagemann 1979
Octanol/water partition coefficient (K_{ow})	2,230	Shatkin and Brown 1991

[a]Taken from Shatkin and Brown 1991. All parameters used were either taken from published experimental work of others or calculated from previously reported mathematical relationships.

NG = value not given

for ingestion of 2 L of water at the same concentration, or from inhalation during a 20-minute shower (Shatkin and Brown 1991). The model may be useful in predicting absorbed doses of ethylbenzene resulting from bathing, swimming, and other activities (Shatkin and Brown 1991).

Target Tissues. The Shatkin and Brown (1991) model was developed to simulate dermal absorption of ethylbenzene (and other volatile organics); it does not predict concentrations of ethylbenzene in specific tissues, other than skin. However, if the model were integrated into PBPK models of the distribution and elimination of absorbed ethylbenzene (e.g., Dennison et al. 2003; Tardif et al. 1997), the combined models might be useful for predicting internal doses of ethylbenzene associated with dermal exposures.

Species Extrapolation. The Shatkin and Brown (1991) model was developed to simulate dermal absorption of ethylbenzene in humans and has been evaluated with observations in humans. The major physiological parameters in the model are scalable or could be determined in different species (e.g., dermal thickness, dermal fat content, dermal blood flow), and the chemical parameters could be evaluated in other species (e.g., partition coefficients) or predicted from physical-chemical properties (e.g., diffusion coefficients). These features improve the feasibility of scaling the model to other species.

Interroute Extrapolation. The Shatkin and Brown (1991) model, in combination with existing PBPK ethylbenzene inhalation models (e.g., Dennison et al. 2003; Tardif et al. 1997), may have utility for estimating dermal exposures (i.e., concentration, time) that would be expected to yield equivalent absorbed doses from inhalation exposures.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Studies of the *in vitro* metabolism of ethylbenzene in microsomes prepared from human liver have identified high and low affinity catalytic pathways for the initial hydroxylation to 1-phenylethanol (Sams et al. 2004). In human liver microsomes, the high affinity pathway exhibited a lower K_m and lower V_{max} (K_m=8 μM, V_{max}=689 pmol/minute/mg protein) than the low affinity pathway (K_m=391 μM, V_{max}=3,039 pmol/min/mg protein) and was inhibited by diethyldithiocarbamate. Studies conducted in microsomes prepared from insect cells expressing recombinant human isoforms of cytochrome P-450 also revealed a relatively high affinity, low V_{max} catalysis by CYP2E1and lower affinity, higher V_{max} catalysis

by CYP1A2 and CYP2B6, suggesting that the latter two isoforms may contribute to the low affinity pathway observed in human liver microsome (Sams et al. 2004).

Blood kinetics of inhaled ethylbenzene have been successfully modeled with assumptions of flow-limited transfer of ethylbenzene to tissues and capacity-limited elimination by metabolism (Dennison et al. 2003, 2004; Tardif et al. 1997, see Section 3.4.5). These models have been successfully scaled from the rat to humans by applying species physiological parameter values (e.g., tissue volumes) and partition coefficients (i.e., blood:air partition coefficient) and allometrically scaling flows (i.e., cardiac output, alveolar ventilation rate) and metabolism parameters (i.e., K_m, V_{max}) to body weight (Tardif et al. 1997). These studies suggest a general similarity of the distribution and elimination kinetics in rats and humans. The robustness of these models for predicting ethylbenzene kinetics in other species has not been reported; however, the blood elimination kinetics of inhaled ethylbenzene in the mouse show similarities to that in the rat (e.g., nonlinearity of clearance with exposure concentration, similar elimination half-times (Charest-Tardif et al. 2006; Tardif et al. 1997).

3.5.2 Mechanisms of Toxicity

Mechanisms of ototoxicity, toxicity to the liver and kidney, and carcinogenicity have not been identified. However, studies on ethylbenzene and ethylbenzene metabolites provide some insights regarding the potential roles of parent compound and metabolites in ethylbenzene-induced effects. As reviewed in Section 3.2.1.4 (Inhalation Exposure, Neurological Effects), inhalation exposure of animals to ethylbenzene produces hearing loss through irreversible loss of OHC in the organ of corti (Cappaert et al. 1999, 2000, 2001, 2002; Gagnaire and Langali 2005; Gagnaire et al. 2007). Cappaert et al. (2002) attributed the lack of ototoxicity (based on auditory thresholds and histological assessment of cochlea) in guinea pigs exposed to inhaled ethylbenzene to lower circulating levels of ethylbenzene, relative to levels producing ototoxicity in rats. Results of a 3-month oral study on phenylglyoxylic acid, a major ethylbenzene metabolite, show that this metabolite did not produce ototoxicity, based on electrophysiological tests, in rats exposed to drinking water at approximately 293 mg/kg/day (Ladefoged et al. 1998). Although this study provides supporting evidence that phenylglyoxylic acid is not ototoxic, animals were not evaluated for OHC loss in this study. Furthermore, Pryor et al. (1991) proposed that hearing loss caused by toluene, which is structurally similar to ethylbenzene, was caused by parent compound, rather than metabolites; pretreatment of rats with phenobarbital, which induces cytochrome P450 metabolism of toluene, prevented ototoxicity. Taken together, results of these studies suggest that ethylbenzene, rather than metabolites, may be responsible for ototoxicity.

Regarding possible mechanisms of carcinogenicity, results of the NTP (1999) bioassay on ethylbenzene provided clear evidence of carcinogenicity in male rats based on renal tubule neoplasms, some evidence in female rats based on renal tubule adenomas, some evidence in male mice based on alveolar/bronchiolar neoplasms, and some evidence in female mice based on hepatocellular neoplasms; in addition, testicular neoplasms were increased in male rats. In contrast, results of an NTP (1990) 2-year bioassay on 1-phenylethanol, a primary oxidative metabolite of ethylbenzene, provided some evidence of carcinogenicity in male rats based on increased incidences of renal tubular cell adenomas and adenomas or adenocarcinoma (combined), but no evidence of carcinogenicity in female rats or male or female mice. These results suggest that carcinogenic activity of ethylbenzene may be, at least in part, attributed to the parent compound and/or reactive oxidative metabolites in the 4-ethylphenol pathway, rather than the 1-phenylethanol pathway.

Ethylbenzene has been shown to exert adverse central nervous system effects on both humans (Yant et al. 1930) and animals (Cragg et al. 1989; Ethylbenzene Producers Association 1986a; Molnar et al. 1986; Tegeris and Balster 1994; Yant et al. 1930). *In vivo* animal studies of ethylbenzene toxicity at the cellular level indicate that changes in brain levels of dopamine and other biochemical alterations, and in evoked electrical activity in the brain may be involved in ethylbenzene central nervous system toxicity (Andersson et al. 1981; Frantik et al. 1994; Mutti et al. 1988; Romanelli et al. 1986).

The molecular mechanism(s) of ethylbenzene-induced ototoxicity has not been established. Results of a recent *in vitro* study suggest that ototoxicity induced by low concentrations of ethylbenzene may be mediated through nicotinic acetylcholine receptors (van Kleef et al. 2008). Using human heteromeric α9α10 nicotinic acetylcholine receptors expressed in *Xenopus* oocytes, ethylbenzene inhibited acetylchloline-mediated ion currents under conditions of low receptor occupancy. Based on *in vitro* studies conducted with toluene, Cappaert et al. (2001) briefly speculated that increased intracellular calcium levels might be responsible for the obliteration of outer hair cells exposed to solvents such as ethylbenzene.

In vitro studies of the mechanism of toxicity have focused on the effect of ethylbenzene on cell membranes, particularly that of the astrocyte (Engelke et al. 1993; Naskali et al. 1993, 1994; Sikkema et al. 1995; Vaalavirta and Tähti 1995a, 1995b). In a review by Sikkema et al. (1995), changes in the structure and integrity of the cell membrane after partitioning of ethylbenzene into the lipid bilayer may be a mechanism of toxicity. Changes in the integrity of the cell membrane may subsequently affect the

function of membrane, particularly as a barrier and in energy transduction, and in the formation of a matrix for proteins and enzymes.

The work of Vaalavirta and Tähti (1995a, 1995b) and Naskali et al. (1993, 1994) has investigated the effect of ethylbenzene on the membrane of the rat astrocyte, as an *in vitro* model for the membrane-mediated effects of solvents on the central nervous system. Cultured astrocytes from the cerebella of neonatal Sprague-Dawley rats were sensitive to the effects of ethylbenzene, as measured by the inhibition of activity of Na+, K+-ATPase, and Mg++-ATPase (Vaalavirta and Tähti 1995a, 1995b). This effect was found to be dose-dependent (Naskali et al. 1994). Inhibition of these membrane-bound enzymes that regulate the ion channels of the membrane may disturb the ability of the cells to maintain homeostasis. Experiments with rat synaptosome preparations, similar to those using microsomal preparations by Engelke et al. (1993), showed that membrane fluidity was increased after exposure to ethylbenzene. ATPase and acetylcholinesterase activity were also decreased, as seen in the astrocyte preparations.

3.5.3 Animal-to-Human Extrapolations

Species differences have been shown for ethylbenzene metabolism. In humans exposed via inhalation, the major metabolites of ethylbenzene are mandelic acid (approximately 70% of the absorbed dose) and phenylglyoxylic acid (approximately 25% of the absorbed dose), which are excreted in the urine (Bardodej and Bardodejova 1970; Engstrom et al. 1984). Evidence indicates that the initial step in this metabolic pathway is oxidation of the side chain of ethylbenzene to produce 1-phenylethanol. In rats exposed by inhalation or orally to ethylbenzene, the major metabolites were identified as hippuric and benzoic acids (approximately 38%), 1-phenylethanol (approximately 25%), and mandelic acid (approximately 15–23%), with phenylglyoxylic acid making up only 10% of the metabolites (Climie et al. 1983; Engstrom et al. 1984, 1985). In rabbits, the most important metabolite is hippuric acid, which is probably formed by oxidative decarboxylation of phenylglyoxylic acid (El Masri et al. 1958). Rabbits have been shown to excrete higher levels of glucuonidated metabolites than do humans or rats (El Masry et al. 1956; Smith et al. 1954a, 1954b). Thus, there are no animal models of ethylbenzene metabolism that are completely consistent with human metabolism. However, of the experimental models investigated, rats appear to be a more appropriate model than rabbits.

Models of the pharmacokinetic mechanisms and mechanisms of toxicity of ethylbenzene have focused on cellular processes (see Sections 3.5.1 and 3.5.2, above). In these, humans and animals appear to be similar. Although some species differences exist with respect to toxicity, adverse effects observed after

ethylbenzene exposure in both humans and animals seem to be similar in scope (i.e., respiratory, hepatic, renal, and neurological). Rats may be more sensitive than mice or rabbits (Cragg et al. 1989; NTP 1992). Thus, the rat may be the most appropriate animal model for studying the mechanism of toxicity of ethylbenzene as it relates to human health effects assessment.

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 1997b). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to ethylbenzene. Nishihara et al. (2000) concluded that ethylbenzene was not estrogenic as established in an *in vitro* yeast two-hybrid assay. No additional *in vitro* studies were located regarding endocrine disruption of ethylbenzene.

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).

There are no data describing the effect of exposure to ethylbenzene in children. Respiratory and eye irritation, and dizziness are the most prevalent signs of exposure to high levels of ethylbenzene (Yant et al. 1930), and it is expected that children would also exhibit these effects, as well as other effects observed in adults. Minor birth defects have occurred in newborn rats, but not rabbits, whose mothers were exposed by breathing air contaminated with ethylbenzene (NIOSH 1981; Ungváry and Tátrai 1985). These defects consisted of urinary tract anomalies (not specified) and supernumerary ribs. Supernumerary ribs were observed in the presence of minimal maternal changes. Although developmental effects were reported in the offspring of animals exposed to <500 ppm ethylbenzene (Ungváry and Tátrai 1985) several longer duration studies have shown developmental effects at biologically or statistically significant levels only in the offspring of rats exposed to >500 ppm ethylbenzene (Faber et al. 2006, 2007; Saillenfait et al. 2003, 2006, 2007). Furthermore, the report by Ungváry and Tátrai (1985) lacks pertinent experimental details, including specific data on the urinary tract anomalies, dictating caution in the interpretation of study findings. Section 3.2.1.6, Developmental Effects, contains a more detailed discussion of these results. It is not known whether these developmental effects observed in animals would be observed in people. Ethylbenzene has been detected in human breast milk at unspecified concentrations (Pellizzari et al. 1982), but no pharmacokinetic experiments have been done to confirm that it is actually transferred to breast milk in mammals. No specific information was found concerning ethylbenzene concentrations in placenta, cord blood, or amniotic fluid.

Since there is no information about health effects in children, it is unknown whether they differ from adults in their susceptibility to health effects from ethylbenzene. However, in general, the principle that early-in-life exposures may increases susceptibility to carcinogens may apply to ethylbenzene (EPA 2005).

There is no specific information about the metabolism of ethylbenzene in children or immature adults. However, since two of the enzyme families responsible for the conjugation and elimination of ethylbenzene metabolites are developmentally regulated, it is possible that the activity of these enzymes would differ in children or immature animals compared to adults. In humans, UDP glucuronosyltransferase activity does not reach adult levels until about 6–18 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases (which is also isoform specific) seems to develop earlier. The activity of some sulfotransferase isoforms may even be greater during infancy and early childhood than in adulthood (Leeder and Kearns 1997). In addition, age-dependence of elimination kinetics (e.g., glomerular filtration and tubular secretion of organic anion metabolites of ethylbenzene), potentially, could contribute to age-related differences in sensitivity to ethylbenzene.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

(e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to ethylbenzene 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 ethylbenzene 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 Ethylbenzene

Information on ethylbenzene concentrations in human tissue or fluids is available. Exposure to ethylbenzene may be determined by the detection of mandelic acid and phenylglyoxylic acid in urine (Bardodej and Bardodejova 1970) or by direct detection of ethylbenzene in whole human blood (Antoine et al. 1986; Ashley et al. 1992; Cramer et al. 1988) or urine (Wang et al. 2007). However, mandelic acid and phenylglyoxilic acid are also metabolites of styrene (Agency for Toxic Substances and Disease Registry 1992).

The 1982 National Human Adipose Tissue Survey conducted by EPA measured ethylbenzene in 96% of the 46 composite samples analyzed for volatile organic compounds (EPA 1986). A wet tissue concentration range of not detected (detection limit=2 ng/g) to 280 ng/g was reported, but an average concentration was not provided.

Numerous studies indicate that environmental exposures to ethylbenzene can result in detectable levels in human tissues (Antoine et al. 1986; Cramer et al. 1988; Pellizzari et al. 1982; Wolff 1976; Wolff et

al. 1977) and in expired air (Conkle et al. 1975; Engstrom and Bjurstrom 1978; EPA 1984e). Analysis of blood specimens from a test population of 250 patients (Antoine et al. 1986) and composite samples obtained from blood donations of laboratory personnel with potentially low-level exposure (Cramer et al. 1988) indicated ethylbenzene concentrations in the blood to range from below detection limits to 59 ppb. Similarly, ethylbenzene was detected in 8 of 12 milk samples from lactating women living in various urban areas of the United States with high probability of emissions of pollutants (Pellizzari et al. 1982). Subcutaneous fat samples taken from individuals exposed to an average of 1–3 ppm ethylbenzene in the workplace contained ethylbenzene levels as high as 0.7 ppm (Wolff 1976; Wolff et al. 1977).

Studies examining the correlation of ethylbenzene concentrations in ambient air with concentrations measured in expired or alveolar air have also been conducted (Conkle et al. 1975; Engstrom and Bjurstrom 1978; EPA 1984e). Ethylbenzene concentrations in breath samples were reported to correlate well with ethylbenzene concentrations in indoor samples taken with personal air monitors (EPA 1984e). A correlation was also found between ethylbenzene uptake and ethylbenzene concentrations in alveolar air during, but not after, inhalation exposure in volunteers (Engstrom and Bjurstrom 1978). Rates of ethylbenzene expiration measured in volunteers with no known previous exposure to ethylbenzene ranged from 0.78 to 14 μg/hour, with higher rates detected in smokers than in nonsmokers (Conkle et al. 1975).

3.8.2 Biomarkers Used to Characterize Effects Caused by Ethylbenzene

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (Agency for Toxic Substances and Disease Registry 1990) and for information on biomarkers for neurological effects see OTA (1990).

No specific biomarkers of effect for ethylbenzene were identified. Most of the information on humans is from case reports in which the effects are general and non-specific, such as eye and throat irritation and chest constriction (Yant et al. 1930).

3.9 INTERACTIONS WITH OTHER CHEMICALS

The metabolism of ethylbenzene includes pathways involving mono-oxygenases (e.g., cytochrome P-450) and formation of glucuronide and sulfate conjugates. Therefore, the metabolism of ethylbenzene could be markedly altered by inhibitors (e.g., carbon monoxide, SKF 525A) and inducers (e.g., phenobarbital, described above) of drug-metabolizing enzymes (Gillette et al. 1974) and by the availability of conjugation reactants (e.g., glucuronic acid, sulfate) that facilitate the excretion of ethylbenzene

metabolites. Mono-oxygenases (MOs) are a class of enzymes involved in the detoxication of xenobiotics, including ethylbenzene. Substances that induce or inhibit MO enzymes may alter the toxicity of ethylbenzene by increasing the rate of production of its metabolites. Compounds that affect glucuronic acid availability could also affect the excretion rate of ethylbenzene metabolites.

Numerous studies have demonstrated interactions between ethylbenzene and chemicals that inhibit cytochrome P-450 (e.g., carbon monoxide; Maylin et al. 1973), compete with ethylbenzene for metabolism by cytochrome P-450 (e.g., alkylbenzenes, ethanol; Angerer and Lehnert 1979; Elovaara et al. 1984; Engstrom et al. 1984; Romer et al. 1986), or induce cytochrome P-450 (e.g. phenobarbital; Maylin et al. 1973; McMahon and Sullivan 1966). Competitive inhibition of metabolism by alkylbenzenes, including ethylbenzene, has been introduced into PBPK models of alkylbenzene mixtures and gasoline component mixtures (Dennison et al. 2003, 2004; Haddad et al. 2001; Tardif et al. 1997).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Even though ethylbenzene is not known to bioaccumulate (Aster 1995; Meylan et al. 1999; Nuns and Benville 1979; Ogata et al. 1984), human and animal studies suggest that several factors can contribute to an increased probability of adverse health effects following ethylbenzene exposure (NIOSH/OSHA 1978). Exposure to ethylbenzene has been shown to produce hearing loss and animals; therefore, individuals with pre-existing hearing loss (e.g., congenital or infection-related) or individuals participating in activities that may result in hearing loss (e.g., sharpshooting) may be more susceptible to the ototoxic effects of ethylbenzene. Exposure of individuals with impaired pulmonary function to ethylbenzene in air has been shown to exacerbate symptoms because of ethylbenzene's irritant properties. Because ethylbenzene is detoxified primarily in the liver and excreted by the kidney, individuals with liver or kidney disease might be more susceptible to ethylbenzene toxicity, as would persons taking medications or other drugs (e.g., alcohol) that are known hepatotoxins. Persons with dermatitis or other

skin diseases may be at greater risk, since ethylbenzene is a defatting agent and may aggravate these symptoms. Children's susceptibility is discussed in Section 3.7.

In summary, groups that might be more susceptible to the toxic effects of ethylbenzene are individuals with hearing loss and diseases of the respiratory system, liver, kidney, or skin; young children; fetuses; pregnant women; and individuals taking certain medications such as hepatotoxic medications or drugs.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to ethylbenzene. 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 ethylbenzene. 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 ethylbenzene:

Leikin JB, Poloucek FP. 2002. Poisoning and toxicology handbook. Hudson, OH: Lexi-Comp, Inc., 554.

Proctor NH, Hughes JP. 1978. Chemical hazards of the workplace. Philadelphia, PA: J.B. Lippincott Company, 251-252.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to ethylbenzene can occur by inhalation, oral, or dermal contact. General recommendations for reducing absorption of ethylbenzene following exposure include removing the exposed individual from the contaminated area and removing the contaminated clothing. Removal of the patient from the source of contamination is an initial priority along with proper ventilation and cardiac monitoring. If the eyes and skin were exposed, they should be flushed with water. Emesis or lavage is not recommended following oral exposure due to the risk of aspiration pneumonia (Leikin and Paloucek 2002). Activated charcoal may be administered to adsorb ethylbenzene (Leikin and Paloucek 2002). Benzodiazepines may be used to control seizures (Leikin and Paloucek 2002). Administration of catecholamines should be avoided due to the risk of ventricular arrhythmia (Leikin and Paloucek 2002).

3.11.2 Reducing Body Burden

Following absorption into the blood, ethylbenzene is rapidly distributed throughout the body. The initial stage of ethylbenzene metabolism in humans is the formation of 1-phenylethanol via hydroxylation of the of the side chain. Further oxidation leads to the formation of mandelic acid and phenylglyoxylic acid, the major urinary metabolites of ethylbenzene in humans. Detoxication pathways generally involve the formation of glucuronide or sulfate conjugates of 1-phenylethanol or its subsequent metabolites. Urinary excretion is the primary route of elimination of metabolized ethylbenzene. Studies in humans and animals indicate that urinary excretion occurs in several phases, with half-lives of hours. Hence, ethylbenzene and its metabolites have relatively short half-lives in the body, and while some of these metabolites are clearly toxic, substantial body burdens are not expected.

No methods are currently used for reducing the body burden of ethylbenzene. It is possible that methods could be developed to enhance the detoxication and elimination pathways.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Treatments interfering with the mechanism of action for toxic effects have not been identified.

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 ethylbenzene 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 ethylbenzene.

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 Ethylbenzene

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

Figure 3-6 graphically describes the existing health effects information on ethylbenzene by route and duration of exposure. Little information concerning humans exposed via inhalation to ethylbenzene is available. Most of the information concerning health effects in humans is reported in occupational studies, which are difficult to interpret given the limitations of the studies (e.g., simultaneous exposure to other hazardous substances, unquantified exposure concentrations, and exposure probably occurring by a combination of routes). No data were available concerning human health effects following oral exposures to ethylbenzene. Dermal effects in humans exposed to ethylbenzene vapors include respiratory and ocular irritation.

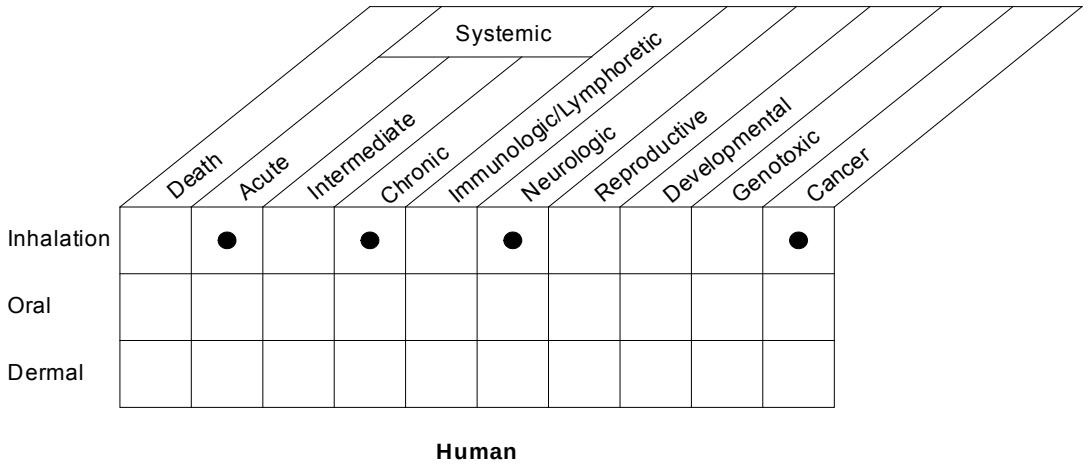
In animals, the lethality of ethylbenzene is documented for all routes of exposure. Systemic, immunologic, neurologic, developmental, and reproductive effects have been reported following acute-, intermediate-, or chronic-duration inhalation exposures to ethylbenzene. Limited data on the health effects resulting from oral or dermal exposure to ethylbenzene were located.

3.12.2 Identification of Data Needs

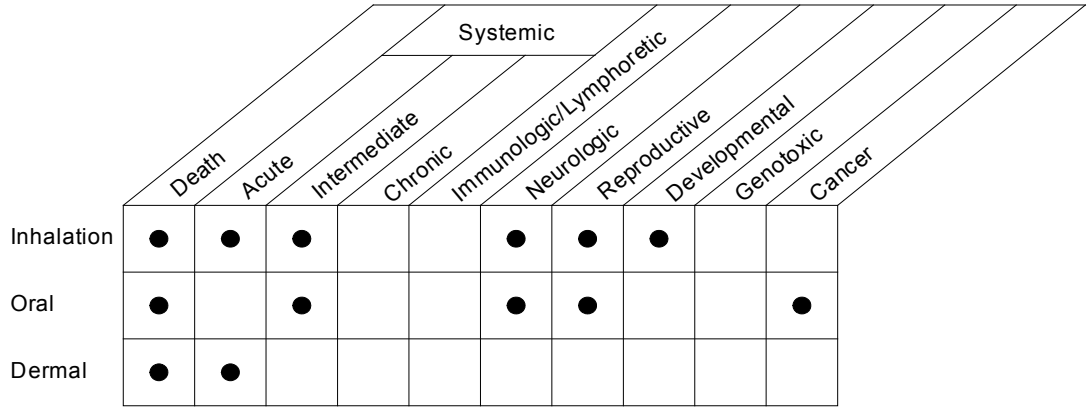
In general, data on the toxic effects of ethylbenzene in humans and animals are limited. In many areas for which studies have been conducted, the lack of reliable data precludes any definitive conclusions from being drawn.

Acute-Duration Exposure. The database for acute-duration inhalation exposure to ethylbenzene is largely composed of inhalation studies in laboratory animals with a limited number of human studies.

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



Human



Animal

● Existing Studies

The available acute-duration studies in humans (Sliwinska-Kowalska et al. 2001; Yant et al. 1930) and animals (Andersson et al. 1981; Cappaert et al. 1999, 2000, 2001, 2002; Ethylbenzene Producers Association 1986a; Molnar et al. 1986; Tegeris and Balster 1994; Yant et al. 1930) indicate that the nervous system, and particularly the auditory system, is sensitive to the toxic effects of ethylbenzene. The available reports and studies in humans are of limited use for dose-response assessment because insufficient information was provided to clearly characterize the exposure to ethylbenzene or because exposures were for mixtures of solvents, not ethylbenzene alone. Ethylbenzene is an acute ocular and respiratory irritant in humans (Cometto-Muñiz and Cain 1995; Thienes and Haley 1972; Yant et al. 1930); however, animal studies suggest that acute sublethal inhalation exposures do not result in pulmonary histopathology (Ethylbenzene Producers Association 1986a). Developmental and reproductive effects were reported in animals exposed to ethylbenzene by inhalation during gestation (Ungváry and Tátrai 1985); however, the latter study is limited by incomplete description of the results and the absence of an analysis on a per litter basis. Increased organ weight (liver, kidneys) has been observed in a number of studies in animals (Ethylbenzene Producers Association 1986a; Toftgard and Nilsen 1982); however, no findings are made upon microscopic examination of the liver or kidneys (Ethylbenzene Producers Association 1986a). An acute-duration inhalation MRL was derived based on ototoxicity in animals. No studies describing acute-duration oral exposure of humans to ethylbenzene were found in the literature. Although two animal studies have examined the acute oral toxicity of ethylbenzene (Gagnaire and Langlais 2005; Ungvary 1986), they were not adequate for the derivation of an acute-duration oral MRL. Mild irritation (Smyth et al. 1962), reddening, exfoliation, and blistering (Wolf et al. 1956) have been reported in rabbits when ethylbenzene was applied directly on the skin. Slight irritation of the eye (Wolf et al. 1956) and corneal injuries (Smyth et al. 1962; Wolf et al. 1956) were observed in rabbits when ethylbenzene was instilled onto the eyes. There is a data need for additional acute-duration oral and dermal toxicity studies in animals exposed to ethylbenzene.

Intermediate-Duration Exposure. The database of intermediate-duration inhalation studies includes several studies in animals, but no studies in humans. It has been shown that the auditory system is sensitive to the toxic effects of ethylbenzene after intermediate-duration inhalation exposure (Gagnaire et al. 2007). Systemic effects have been observed at concentrations equal to or higher than those that elicited ototoxic effects in rats. Effects at even higher concentrations include neurological and hematological effects (Cragg et al. 1989; Wolf et al. 1956) and increased organ weight (Cragg et al. 1989; Elovaara et al. 1985; NIOSH 1981; NTP 1992; Wolf et al. 1956). Organs showing increased weight did not show treatment-related histopathological effects (Cragg et al. 1989; NTP 1992). Developmental and/or reproductive effects have been reported in offspring of animals following intermediate-duration

inhalation exposures to ethylbenzene during gestation (Faber et al. 2006, 2007; NIOSH 1981; Saillenfait et al. 2003, 2006, 2007) at concentrations that were higher than those that elicited ototoxic effects. An intermediate-duration inhalation MRL was derived based on the observed ototoxic effects in animals (Gagnaire et al. 2007). The intermediate-duration oral database for ethylbenzene is limited to the critical study by Mellert et al. (2007) evaluating the effects of oral exposure of rats to ethylbezene for 4 and 13 weeks, and a poorly reported 6-month exposure study in rats (Wolf et al. 1956). Results of the 13-week gavage study in rats observed effects indicative of liver toxicity, including increased activity of serum liver enzymes (alanine aminotransferase and γ-glutamyl transferase), increased absolute and relative liver weights, and a dose-related increase in the incidence of centrilobular hepatocyte hypertrophy. Results of the 4-week exposure study in rats are similar to those observed in the 13-week study, showing that the liver is the primary target organ for oral ethylbenzene; effects consistent with hepatotoxicity, including increased absolute and relative liver weights, increased incidence of hepatocyte centrilobular, and increased serum liver enzyme activity (alanine aminotransferase) (Mellert et al. 2007). Wolf et al. (1956) reported slight weight and histopathological effects in the liver and kidney of female rats. An intermediate-duration oral MRL was derived based on the observed liver effects in animals exposed for 13 weeks (Mellert et al. 2007).

Chronic-Duration Exposure and Cancer. The database of chronic-duration/carcinogenicity inhalation studies with ethylbenzene includes a chronic duration study in rats and mice (NTP 1999) and a limited number of studies in humans. Hematological effects were observed in workers exposed to solvents containing ethylbenzene (Angerer and Wulf 1985), but no hematological effects, liver lesions or effects on liver function, or cases of malignancy were reported in a study of workers exposed chronically (>20 years) to ethylbenzene (Bardodej and Cirek 1988). The severity of nephropathy was significantly increased in female and male rats exposed to ≥75 or 750 ppm ethylbenzene, respectively, for 2 years (NTP 1999). At higher concentrations rats showed significant increases in renal tubule hyperplasia; male rats showed an increased incidence of interstitial cell adenoma in the testis. Effects observed in male or female mice exposed to ethylbenzene for 2 years include an increased incidence of hyperplasia of the pituitary gland pars distalis, increased incidence of follicular cell hyperplasia in the thyroid gland, an increased incidence of syncytial alterations of the hepatocytes, hypertrophy, and hepatic necrosis, and an increased incidence of eosinophilic foci (NTP 1999). Ethylbenzene showed clear evidence of carcinogenic activity in male rats based on increased incidences of renal tubule neoplasms, some evidence of carcinogenic activity in female rats based on increased incidences of renal tubule adenomas, some evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms, and some evidence of carcinogenic activity in female mice based on increased incidences of

hepatocellular neoplasms (NTP 1999). The 2-year inhalation study in rats suggests that an increase in the severity of nephropathy in female rats is the most sensitive end point of ethylbenzene exposure. This end point was selected to estimate a chronic-duration inhalation MRL. There is no need to conduct additional carcinogenicity studies of ethylbenzene via inhalation. A statistically significant increase in total malignant tumors was reported in female rats and in combined male and female groups exposed to 500 mg kg/day via gavage for 104 weeks (Maltoni et al. 1985). No data on specific tumor type were presented, only one dose was tested, and no information on survival was provided. It might be useful to conduct a toxicity and carcinogenicity study of ethylbenzene administered orally to at least two animal species. It might be useful to conduct chronic-duration studies in at least two species with an emphasis in ototoxic effects.

Genotoxicity. There are limited data on the genotoxicity of ethylbenzene in humans. Two studies examined potential genotoxic effects in workers (Holz et al. 1995; Sram et al. 2004); the interpretation of these results is limited by co-exposure to other chemicals (e.g., benzene, toluene, styrene). *In vivo* genotoxicity studies in laboratory animals did not cause significant alterations in micronuclei formation (Mohtashamipur et al. 1985; NTP 1992, 1999) or unscheduled DNA syntheseis (Clay 2001). Data are available regarding the genotoxic potential of ethylbenzene from *in vitro* assays in bacteria, yeast, and mammalian cell cultures (Dean et al. 1985; Degirmenci et al. 2000; Florin et al. 1980; Kubo et al. 2002; Nestmann and Lee 1983; Nestmann et al. 1980; NTP 1986, 1999; Zeiger et al. 1992). The results generally indicate that ethylbenzene is not mutagenic. Similarly, *in vitro* genotoxic assays in mammalian cells were negative when noncytotoxic concentrations were used (Dean et al. 1985; McGregor et al. 1988; NTP 1986, 1999; Seidel et al. 2006; Wollny 2000). However, some studies did not cause genotoxic alterations at concentrations not associated with cytotoxicity (Chen et al. 2008; Gibson et al. 1997); it is not known whether these positive results reflect a genotoxic response in a particular test system or whether they are outliers. Independent confirmation or refutation of these studies, as well as further genotoxicity studies, especially in mammalian systems, would help provide clarification of these conflicting results.

Reproductive Toxicity. No studies were located regarding reproductive effects in humans following inhalation exposure to ethylbenzene. Reproductive end points have been assessed after acute- (Ungváry and Tátrai 1985) and intermediate-duration exposures of animals exposed during gestation (Saillenfait et al. 2003, 2006, 2007) and in a two-generation reproductive toxicity study (Faber et al. 2006, 2007). Effects on reproductive organs (Cragg et al. 1989; NTP 1992, 1999; Wolf et al. 1956) in animals exposed to ethylbenzene have also been evaluated. The only available oral-exposure reproduction study reported

decreased hormone levels and blockage or delay of the estrus cycle in female rats (Ungvary 1986). Additional inhalation exposure reproductive toxicity studies are not deemed necessary at this time. It might be useful to conduct additional oral exposure reproductive toxicity studies in at least two species.

Developmental Toxicity. No studies of developmental effects in humans following inhalation exposure to ethylbenzene were located. The available studies have reported developmental effects in the offspring of animals exposed to ethylbenzene during gestation (NIOSH 1981; Saillenfait et al. 2003, 2006, 2007; Ungváry and Tátrai 1985). The report by Ungváry and Tátrai (1985) has many deficiencies, including poor reporting of the experimental conditions and poor description of the maternal and fetal observations. Maternal toxicity has been generally reported at the highest doses tested (Saillenfait et al. 2003, 2006, 2007; Ungváry and Tátrai 1985). Biologically or statistically significant developmental or neurodevelopmental effects were not observed in the offspring of animals in a two-generation inhalation study (Faber et al. 2006, 2007). No studies were located regarding developmental effects in humans and animals following oral or dermal exposure to ethylbenzene. A data need exists for oral and dermal developmental toxicity studies.

Immunotoxicity. No studies were found regarding immunological effects in humans following inhalation exposure to ethylbenzene. No effects on humoral immune function were observed in female rats exposed to ethylbenzene vapor for 28 days (Stump 2004). Studies also were located that examined organs of the immune system in animals after intermediate- (Cragg et al. 1989; NIOSH 1981; NTP 1992) or chronic-duration (NTP 1999) exposure to ethylbenzene. No studies were located regarding immunological effects in humans or animals following oral or dermal exposure to ethylbenzene. No additional immunological studies are deemed to be necessary at this time.

Neurotoxicity. Human studies have established that acute exposure to ethylbenzene may result in dizziness and vertigo (Yant et al. 1930) and that hearing loss is significantly increased in workers exposed to solvent mixtures that include ethylbenzene (Sliwinska-Kowalska et al. 2001). The role of ethylbenzene in the observed hearing losses cannot be ascertained from this study given that ethylbenzene was only one of several solvents.

Animal studies indicate that the auditory system is the most sensitive target of ethylbenzene toxicity after acute- (Cappaert et al. 1999, 2000, 2001, 2002) or intermediate-duration (Gagnaire et al. 2007) inhalation exposures and after acute-duration oral exposures to ethylbenzene (Gagnaire and Langlais 2005). The effects of ethylbenzene on the central nervous system have been assessed in animals after acute-duration

exposure to ethylbenzene (Ethylbenzene Producers Association 1986a; Molnar et al. 1986; Tegeris and Balster 1994; Yant et al. 1930). Neurobiochemical and electrical activity alterations have been reported in animals after acute-duration exposure to ethylbenzene (Andersson et al. 1981; Frantik et al. 1994; Mutti et al. 1988; Romanelli et al. 1986). No adverse histopathological findings were observed in brain tissue of animals after intermediate- (NTP 1992) or chronic-duration (NTP 1999) exposure to ethylbenzene. No studies were located regarding neurological effects in humans following oral exposure to ethylbenzene. Ototoxicity is also observed in animals after acute-duration oral exposure to ethylbenzene (Gagnaire and Langlais 2005). Additional studies are needed to establish the mechanism of action by which ethylbenzene elicits ototoxicity, as no information establishing the mechanism of ethylbenzene-induced ototoxicity was identified. Furthermore, due to the large differences between rats and guinea pigs in susceptibility to ethylbenzene-induced ototoxicity, additional studies on hearing and ear physiology in rodents are needed to evaluate which species is most similar to humans. No studies were located regarding neurological effects in humans or animals following dermal exposure to ethylbenzene. Additional inhalation studies are needed to establish an intermediate-duration NOAEL for ototoxic effects. Additional studies are also needed to characterize the concentration-response pattern for ototoxicity after acute- and intermediate-duration oral exposures to ethylbenzene.

Epidemiological and Human Dosimetry Studies. The few available epidemiological studies on the health effects of ethylbenzene were primarily limited to occupational studies in which quantitative estimates of exposure were lacking and other limitations (e.g., multiple exposure routes, simultaneous exposure to other hazardous chemicals) were present. Studies using volunteers exposed to low concentrations of ethylbenzene have provided useful information on effects of acute-duration inhalation exposure on the central nervous system (Yant et al. 1930). No studies were available in which humans were exposed orally or dermally to ethylbenzene. Epidemiological studies conducted in populations exposed to ethylbenzene alone may provide useful information on the effects of ethylbenzene in humans. Emphasis should be placed in the detection of ototoxic effects as this end point is the most sensitive effect observed in animal studies.

Biomarkers of Exposure and Effect. Sensitive methods are available for determining ethylbenzene and ethylbenzene metabolites in biological tissues and fluids. However, limited data are available associating levels of ethylbenzene in human tissues and fluids with adverse health effects. Additional animal or epidemiological studies evaluating the association between levels in tissue or fluids and adverse health effects would be useful to devise more sensitive and more specific early biomarkers of effect.

Exposure. Exposure to ethylbenzene can be monitored through levels of ethylbenzene in breath, blood, or tissue, or levels of its metabolites, mandelic or phenylglyoxylic acid in urine. A statistically significant correlation was observed between urinary excretion of mandelic acid and ethylbenzene exposure in workers exposed to mixed solvents (including an ethylbenzene TWA of 0.9 ppm) in a metal-coating factory (Kawai et al. 1991). However, neither one of the metabolites is specific to ethylbenzene. Additional studies to identify a biomarker or biomarkers of exposure specific to ethylbenzene are needed.

Effect. There are currently no known specific biomarkers of effect for ethylbenzene. Development of methods to identify biomarkers that would indicate toxic effects, and the extent of those toxic effects after exposure to ethylbenzene, would be helpful in managing health effects that occur after significant exposure to ethylbenzene.

Absorption, Distribution, Metabolism, and Excretion. Ethylbenzene is absorbed by humans following inhalation (Bardodej and Bardodejova 1970; Gromiec and Piotrowski 1984) and dermal (Dutkiewicz and Tyras 1967) exposures. Absorption rates were 49–64% by inhalation. Dermal absorption rates were in the range of 24–33 and 0.11–0.23 mg/cm^2/hour for male subjects exposed to liquid ethylbenzene and ethylbenzene from aqueous solutions, respectively (Dutkiewicz and Tyras 1967). Animal data support these findings and indicate that absorption rates are high following oral exposures as well (Climie et al. 1983; El Masry et al. 1956).

Only one study (Engstrom and Bjurstrom 1978) is available that outlines the distribution of ethylbenzene in humans following inhalation exposure. This study indicates rapid distribution to adipose tissues throughout the body. Inhalation studies in animals support these results (Elovaara et al. 1982; Engstrom et al. 1985). Ethylbenzene is accumulated primarily in the intestine, liver, kidney, and fat, which provides some basis for ethylbenzene-induced effects observed in the liver and kidney. No data on distribution of ethylbenzene following dermal exposure were located. Such information would be useful because absorption of liquid ethylbenzene via this route is rapid in humans and because the potential exists in humans for dermal exposure.

The metabolism of ethylbenzene in humans and animals has been studied. Although some differences in the metabolic pattern according to route of exposure, sex, nutritional status (Nakajima and Sato 1979), and species (Bakke and Scheline 1970; Climie et al. 1983; El Masry et al. 1956; Engstrom et al. 1984, 1985; Smith et al. 1954a, 1954b; Sollenberg et al. 1985) have been documented, pharmacokinetic data

show no significant differences in metabolism between oral and inhalation routes in either humans or animals (Climie et al. 1983; Engstrom et al. 1984, 1985). Further studies that correlate these differences in metabolism with differences in health effects would be useful. Data on metabolism following dermal exposure are sparse, because it is difficult to accurately measure absorption of volatile compounds. Additional data on metabolism following dermal exposure would be useful as these exposures could occur both from contaminated soil or groundwater.

Ethylbenzene has been shown to be rapidly eliminated from the body following inhalation exposure (primarily in the urine) in both humans and animals. These studies (Gromiec and Piotrowski 1984; Yamasaki 1984) are sufficient to characterize the elimination of ethylbenzene following inhalation exposure. A small number of studies in animals exposed orally and humans exposed dermally support these findings. Further studies on elimination of ethylbenzene via these exposure routes would be useful, especially because differences in the excretion patterns have been observed with different routes of exposure.

PBPK models have been developed for predicting ethylbenzene kinetics (including metabolism) in rats and humans exposed by inhalation (Dennison et al. 2003, 2004; Tardif et al. 1997) and in rats exposed to gavage doses of ethylbenzene in corn oil (Faber et al. 2006).

Comparative Toxicokinetics. Quantitative and qualitative variations in the absorption, distribution, metabolism, and excretion of ethylbenzene were observed depending on exposure routes, sex, nutritional status, and species, as previously outlined. Further studies that focus on these differences and their implications for human health would be useful. Additionally, *in vitro* studies using human tissue and PBPK modeling would contribute significantly to the understanding of the kinetics of ethylbenzene, since they would provide information on half-lives and saturation kinetics associated with the metabolism of ethylbenzene.

Methods for Reducing Toxic Effects. No information was found that specifically addressed the reduction of toxic effects after absorption of ethylbenzene. Development of clinical procedures for minimizing the effects of ethylbenzene on the respiratory, hepatic, and renal systems, and the central nervous system would be useful in situations where significant exposure had occurred.

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.

There are no data describing the effects of ethylbenzene exposure in children or developing postnatal animals. Data needs relating to development are discussed in more detail above under developmental effects. In order to evaluate whether ethylbenzene presents a unique hazard to children, additional information on the health effects, pharmacokinetics, metabolism, and mechanism of action in children is needed. It is unknown whether children differ from adults in their susceptibility to health effects from exposure to ethylbenzene. Pharmacokinetic studies investigating whether ethylbenzene or its active metabolites cross the placenta or are transferred into breast milk would be useful. Studies to determine whether there are specific biomarkers of exposure in children would be helpful in monitoring the exposure of children to this chemical. In addition, information describing methods of reducing toxic effects and decreasing body burden in children might be helpful.

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

Ongoing studies pertaining to ethylbenzene have been identified and are shown in Table 3-10 (FEDRIP 2007). In addition, the American Chemistry Council is conducting investigations on the mode of action of ethylbenzene-induced mouse lung tumors, including the role of ethylbenzene ring-oxidation to cytotoxic quinine metabolites.

Table 3-10. Ongoing Studies on Ethylbenzene

Investigator	Affiliation	Research description	Sponsor
Thrall KD	Battelle Pacific Northwest Laboratories	Dermatopharmacokinetics of paint solvents.	National Institute for Occupational safety and Health
Backes WL	Louisiana State University	Identify conditions under which individuals may be susceptible to alkylbenzene-induced toxicity.	National Institute of environmental Health Sciences
Burke J	Environmental Protection Agency	A critical review and probabilistic model input distribution development for microenvironmental exposures to benzene.	Environmental Research Laboratories
Davis-Hoover W	Environmental Protection Agency	Determining if biologically active *in situ* BioNets could bioremediate methyl-*tert*-butyl ether and BTEX contaminated groundwater.	Risk Management Resource Library
Venosa A	Environmental Protection Agency	Treatability of co-mingled groundwater plume contaminated with polycyclic aromatic hydrocarbons.	Risk Management Resource Library
Vroblesky DA	Department of the Interior, U.S. Geological Survey, Water Resources Division	Remediation of JP-4 contamination using hydraulic containment and in situ biodegradation at the Defense Fuel Supply Center, Charleston, South Carolina.	Department of the Interior, U.S. Geological Survey, Water Resources Division
Jayarao BM	Pennsylvania State University, Veterinary Science	Bioreporter-based technology for detection of organic toxicants directly from milk and milk products.	Pennsylvania State University, Veterinary Science
Sylva TY	University of Hawaii, Molecular Biosciences and Biosystems	Application of bioremediation to hydrocarbon contaminated soils.	University of Hawaii, Molecular Biosciences and Biosystems
Holm RH	Harvard University, Department of Chemistry	Transformations catalyzed by the molybdenum and tungsten oxotransferases and hydroxylases.	National Science Foundation
Miknis F	FETC-MGN	Noncatalytic concept for the direct conversion of fossil fuels and hydrocarbon-containing materials to transportation fuels with simultaneous reduction in the heteroatom content.	Office of Fossil Energy
Starr RC	Idaho National Engineering and Environmental Laboratory	Development and testing of an in situ system for remediating groundwater contaminated with BTEX.	Office of Fossil Energy
Friesen DT	Bend Research, Inc.	High-performance membranes for gas, vapor, and liquid separations.	Office of Energy Research

Table 3-10. Ongoing Studies on Ethylbenzene

Investigator	Affiliation	Research description	Sponsor
Sibold J	Golden Technologies Company, Inc.	Investigating the use of ceramic membranes in dehydrogenation reactions.	Energy Efficiency, Department of Energy
Ittrell J	SE, Inc.	Advanced low temperature emissions control technology for MTB destruction.	SE, Inc.
aPierre R	Recision Combustion, Inc	Investigating ano-zeolite coatings on microlith substrates for high selectivity chemical reactions.	Recision Combustion, Inc.

BTEX = benzene, toluene, ethylbenzene, and xylenes

Source: FEDRIP 2007

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4. CHEMICAL AND PHYSICAL INFORMATION

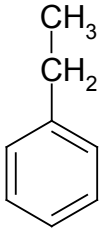
4.1 CHEMICAL IDENTITY

Ethylbenzene is an aromatic hydrocarbon that occurs naturally in petroleum and is a component of aviation and automotive fuels. It is used as a solvent and in the production of synthetic rubber and styrene. Information regarding the chemical identity of ethylbenzene is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Ethylbenzene is a colorless liquid with an aromatic odor. Information regarding the physical and chemical properties of ethylbenzene is located in Table 4-2. Ethylbenzene is a flammable and combustible liquid. Vapors are heavier than air and may travel to a source of ignition and flash back. Liquid ethylbenzene floats on water and may travel to a source of ignition and spread fire. Combustion may produce irritants and toxic gases (HSDB 2009; NFPA 1994). Ethylbenzene may accumulate static electricity and will react with oxidizing materials (HSDB 2009; NFPA 1994).

Table 4-1. Chemical Identity of Ethylbenzene

Characteristic	Information	Reference
Chemical name	Ethylbenzene	Budavari and O'Neil 1989
Synonym(s)	EB; ethyl benzene; benzene, ethyl-; ethylbenzol; phenylethane; etilbenzene; ethylbenzeen; aethylbenzo; etylobenzen	HSDB 2009
Registered trade name(s)	No data	
Chemical formula	C_8H_{10}	Cannella 2007
Chemical structure		Cannella 2007
Identification numbers:		
CAS registry	100-41-4	Cannella 2007
NIOSH RTECS	NIOSH/DA0700000	NIOSH 2009; RTECS 2009
EPA hazardous waste	F003	HSDB 2009
OHM/TADS	7216709	HSDB 1995
DOT/UN/NA/IMDG shipping	UN 1175; IMDG 3.2	HSDB 2009
HSDB	84	HSDB 2009
NCI	NCI-C56393	HSDB 2009
STCC	49 091 63	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; 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; STCC = Standard Transport Commodity Code

Table 4-2. Physical and Chemical Properties of Ethylbenzene

Property	Information	Reference
Molecular weight	106.17	Lide 1994
Color	Colorless	Welch et al. 2005
Physical state	Liquid	Welch et al. 2005
Melting point	-94.975 °C	Cannella 2007
Boiling point	136.19 °C	Cannella 2007
Density at 20 °C/4 °C	0.8670	Welch et al. 2005
at 25 °C/25 °C	0.8671	Cannella 2007
Odor	Sweet, gasoline-like	CHRIS 1985
Odor threshold:		
Water	0.029 mg/L	Amoore and Hautala 1983
	0.140 mg/L	Rosen et al. 1963; Verschueren 1983
Air	2.3 ppm	Amoore and Hautala 1983
	2–2.6 mg/m^3	Verschueren 1983
Solubility:		
Water at 0 °C	197 mg/L	Polak and Lu 1973
at 15 °C	140 mg/L	Verschueren 1983
at 20 °C	152 mg/L	Verschueren 1983
at 25 °C	160 mg/L	Amoore and Hautala 1983
at 25 °C	177 mg/L	Polak and Lu 1973
at 25 °C	208 mg/L	Bohon and Claussen 1951
Organic solvents	Miscible with usual organic solvents	Budavari and O'Neil 1989
	Soluble in alcohol and ether	Lide 1994
Partition coefficients:		
Log K_{ow}	4.34	EPA 1982
	3.13	Yalkowsky and Valvani 1976
	3.15	Hansch et al. 1995
Log K_{oc}	2.22 (calculated)	Chiou et al. 1983
	2.38 (measured)	Hodson and Williams 1988
	2.40 (calculated)	Vowles and Mantoura 1987
Vapor pressure		
at 20 °C	7 mm Hg	Verschueren 1983
at 25 °C	1.27 kPa (9.53 mm Hg)	Mackay and Shiu 1981
at 25.9 °C	10 mm Hg	Sax and Lewis 1989
at 30 °C	12 mm Hg	Verschueren 1983

Table 4-2. Physical and Chemical Properties of Ethylbenzene

Property	Information	Reference
Henry's law constant:		
at 20 °C	$6.6x10^{-3}$ atm-m^3/mol	EPA 1982
at 20 °C	$8.7x10^{-3}$ atm-m^3/mol	Lyman et al. 1982
at 25 °C	$8.43x10^{-3}$ atm-m^3/mol	Mackay et al. 1979
at 25 °C	$7.9x10^{-3}$ atm-m^3/mol	Mackay and Shiu 1981
Autoignition temperature	810 °F (432 °C)	Cannella 2007; NFPA 1994;
Flash point	15 °C	Cannella 2007
Flammability limits	0.8 (lower) vol% –6.7 (upper) vol%	NIOSH 2005
Conversion factors (25 °C, 1 atm)	1 mg/m^3=0.230 ppm 1 ppm=4.34 mg/m^3	NIOSH 2005; Verschueren 1983

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

5.1 PRODUCTION

Ethylbenzene is primarily produced by the alkylation of benzene with ethylene in liquid-phase slurry reactors promoted with aluminum chloride catalysts or by vapor-phase reaction of benzene with dilute ethylene-containing feedstock with a boron trifluoride catalyst supported on alumina (Cannella 2007; Clayton and Clayton 1981; HSDB 2009; Welch et al. 2005; Ransley 1984). Newer versions of the method employ synthetic zeolites in fixed-bed reactors as catalysts for alkylation in the liquid phase or narrow pore synthetic zeolites in fixed-bed reactors in the vapor phase (Welch et al. 2005). Other methods of manufacturing ethylbenzene include preparation from acetophenone, dehydrogenation of naphthenes, catalytic cyclization and aromatization, separation from mixed xylenes via fractionation, reaction of ethylmagnesium bromide and chlorobenzene, extraction from coal oil, and recovery from benzene-toluene-xylene (BTX) processing(Clayton and Clayton 1981; HSDB 2009; Ransley 1984; Welch et al. 2005). Commercial grades of ethylbenzene may contain small amounts of *m*-xylene, *p*-xylene, cumene, and toluene (HSDB 2009).

Ethylbenzene is traditionally ranked as one of the top 50 chemicals produced in the United States. Table 5-1 shows the historical production volumes of ethylbenzene from 1983 to 2005 (C&EN 1994a, 1994b, 1995, 2006; Kirschner 1995).

Table 5-2 lists the facilities in each state that manufacture or process ethylbenzene, the intended use, and the range of maximum amounts of ethylbenzene that are stored on site. There are currently 3,755 facilities that produce, process, or use ethylbenzene in the United States. The data listed in Table 5-2 are derived from the Toxics Release Inventory (TRI06 2008). These data should be used with caution however since only certain types of facilities are required to report (EPA 1995d). Therefore, this is not an exhaustive list.

Currently, there are eight major producers of ethylbenzene in the United States, with a combined annual production capacity of approximately 15.8 billion pounds (SRI 2006). These producers and their respective plant locations are provided in Table 5-3.

Table 5-1. Ethylbenzene Production in the United States from 1983 to 2005

Year	Production in thousands of metric tons	Production in billions of pounds
1983	3,583	7.9
1984	3,447	7.6
1985	3,357	7.4
1986	4,082	9.0
1987	4,218	9.3
1988	4,491	9.9
1989	4,173	9.2
1990	3,810	8.4
1991	5,171	11.4
1992	5,035	11.1
1993	5,352	11.8
1994	5,398	11.9
1995	6,194	13.7
1996	4,699	10.4
1997	5,432	12.0
1998	5,743	12.7
1999	5,945	13.1
2000	5,968	13.2
2001	4,642	10.2
2002	5,412	11.9
2003	5,578	12.3
2004	5,779	12.7
2005	5,251	11.6

Source: C&EN 1994a, 1994b, 1995, 2006; Kirschner 1995

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	21	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12
AL	109	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	50	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AS	1	100,000	999,999	9
AZ	34	100	9,999,999	1, 2, 4, 5, 7, 8, 9, 10, 11, 12, 13
CA	238	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	32	0	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
CT	37	0	999,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	18	0	49,999,999	1, 2, 3, 6, 7, 8, 10, 11, 12, 13
GA	86	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GU	8	100	9,999,999	2, 3, 4, 7, 9, 12
HI	23	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14
IA	56	0	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
ID	4	1,000	999,999	1, 5, 7, 9, 11, 12
IL	156	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	134	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
KS	90	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	91	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
LA	235	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	44	100	499,999,999	1, 2, 4, 5, 7, 8, 9, 10, 11, 12, 14
MD	54	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	17	0	49,999,999	2, 3, 4, 7, 9, 10, 11, 12
MI	185	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	79	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	95	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MP	8	0	999,999	2, 3, 4, 7, 9
MS	73	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	19	10,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
NC	68	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	11	1,000	9,999,999	1, 2, 3, 4, 6, 7, 9, 10, 12
NE	22	0	9,999,999	1, 2, 3, 7, 8, 10, 11, 12
NH	16	0	999,999	2, 7, 9, 10, 11, 12, 13
NJ	102	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	30	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
NV	15	100	999,999	1, 2, 4, 7, 8, 9, 11, 12
NY	85	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	172	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	59	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OR	36	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
PA	145	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	58	100	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
RI	19	0	999,999,999	1, 2, 4, 7, 8, 9, 10, 11, 12
SC	55	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	8	100	99,999	7, 10, 11
TN	81	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	412	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	45	100	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
VA	69	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
VI	9	10,000	49,999,999	1, 2, 3, 4, 6, 7, 8, 9, 12
VT	5	0	999,999	7, 11
WA	69	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	73	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	60	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WY	34	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14

[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)

Table 5-3. Manufacturers and Annual Production Capacity of Ethylbenzene

Manufacturer	Plant location	Annual capacity (millions of pounds)
Chevron Phillips Chemical Company	St. James, Louisiana	2,083
	Pascagoula, Mississippi	289
Cos-Mar Company	Carville, Louisiana	2,822
The Dow Chemical Company	Freeport, Texas	1,896
INEOS America	Texas City, Texas	1,124
Lyondell Chemical Company	Channelview, Texas	3,245
NOVA Chemical Corporation	Bayport, Texas	1,940
Sterling Chemicals Incorporated	Texas City, Texas	1,920
Westlake Styrene Corporation	Sulphur, Louisiana	450
Total capacity		15,769

Source: SRI 2006

5.2 IMPORT/EXPORT

According to the Chemical Marketing Reporter, import volumes were negligible in 2002 and were 4.95×10^7 kg (109 million pounds) in 2003 (CMR 2004). Import volumes for ethylbenzene have been relatively small as compared to annual production, typically representing ≤1% of the annual domestic production volume.

U.S. exports for 2002 and 2003 were reported as 1.86×10^7 kg (41 million pounds) and 1.50×10^7 kg (33 million pounds), respectively (CMR 2004). Export volumes for ethylbenzene have been relatively small, typically representing ≤1% of the annual domestic production volume.

5.3 USE

Ethylbenzene is used primarily as a precursor in the production of styrene (ACGIH 2002; Cannella 2007; Ransley 1984; Verschueren 1983). It is estimated that >99% of the ethylbenzene manufactured in the United States is ultimately used in styrene production, while the remainder is exported or sold in solvent applications (CMR 2004; HSDB 2009; Welch et al. 2005). Ethylbenzene is also used as a solvent, a constituent of asphalt and of naphtha, and in fuels (ACGIH 2002; Verschueren 1983) as well as in the manufacture of acetophenone, cellulose acetate, diethylbenzene, ethyl anthraquinone, ethylbenzene sulfonic acids, propylene oxide, and α-methylbenzyl alcohol (HSDB 2000; Verschueren 1983; Welch et al. 2005).

5.4 DISPOSAL

Regulations governing the treatment and disposal of wastes containing ethylbenzene are detailed in Chapter 8. Recommended methods for the disposal of ethylbenzene include burial in a landfill and rotary kiln incineration, liquid injection incineration, and fluidized bed incineration (EPA 1981d; HSDB 2009). Ethylbenzene may be disposed of by adsorbing it in vermiculite, dry sand, earth, or a similar material and then by burial in a secured sanitary landfill or by atomizing in a suitable combustion chamber (IRPTC 1985). Ethylbenzene is a good candidate for liquid injection incineration at a temperature range of 650–1,600 °C and a residence time of 0.1–2 seconds; a candidate for rotary kiln incineration at a temperature range of 820–1,600 °C and a residence time of seconds for gases and liquids and hours for solids; and a good candidate for fluidized bed incineration at a temperature range of 450–980 °C and a residence time of seconds for gases and liquids, and longer for solids (HSDB 2009).

The following waste water treatment technologies have been investigated for disposal of ethylbenzene; biological treatment, air and steam stripping, or activated carbon treatment (HSDB 2009). Spent ethylbenzene solvents and still bottoms from the recovery of these solvents are designated hazardous wastes and, as such, are subject to the Resource Conservation and Recovery Act (RCRA) of 1976 handling and record-keeping requirements (EPA 1992c).

According to the TRI, in 2006, an estimated 141,972 pounds (64,455 kg) were transferred off-site, which includes releases to publicly owned treatment works (POTWs) (TRI06 2008). No additional information was located on the trends in disposal methods related to ethylbenzene.

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

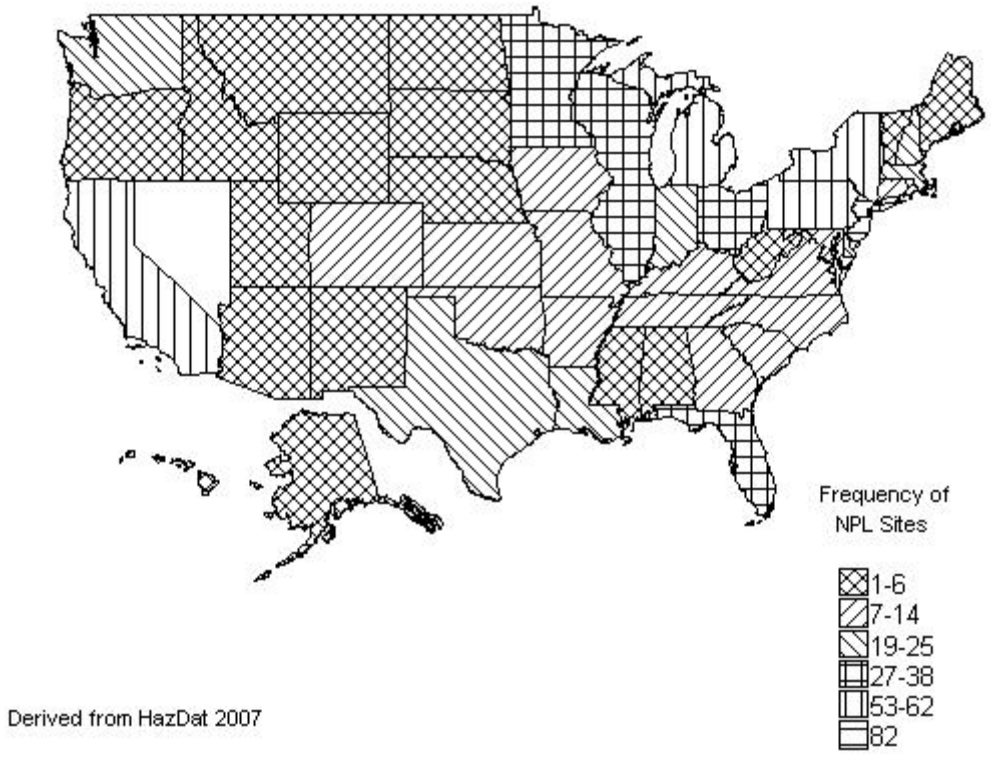
Ethylbenzene has been identified in at least 829 of the 1,689 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for ethylbenzene is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 825 are located within the United States, 2 are located in the Commonwealth of Puerto Rico, and 2 are located in the Virgin Islands (not shown).

Ethylbenzene is an aromatic hydrocarbon naturally present in crude petroleum. It is also a combustion byproduct of biomass. It is widely distributed in the environment because of human activities such as the use of fuels and solvents (which account for the bulk of emissions) and through chemical manufacturing and production activities. Because of its volatile nature, ethylbenzene tends to partition to the atmosphere when it is released to the environment; therefore, exposure to this chemical is most likely to occur by inhalation. However, it is also present in trace amounts in some water supplies and food items. Thus, ingestion also may be an important exposure pathway in some cases. Exposures from contaminated water may also occur via inhalation and dermal absorption during showering and other household activities (Beavers et al. 1996).

Physical, chemical, and biological processes can remove ethylbenzene from the medium of concern and reduce human exposures. In the atmosphere, ethylbenzene exists primarily in the vapor phase. Vapor phase ethylbenzene is removed from air by reacting with photochemically produced hydroxyl radicals, with an approximate half-life of 2 days. Photolytic transformations may also take place in surface water in the presence of naturally occurring humic materials (sensitized photolysis). Biologically induced transformations take place largely in soil and surface water in the presence of oxygen; however, anaerobic degradation can also occur in soil, sediment, and groundwater, but at a much slower rate than aerobic biodegradation. Although chemical transformations can result in reduced exposures to ethylbenzene in the atmosphere, one toxic by-product of ethylbenzene photodegradation, peroxyacetylnitrate (PAN), may be of concern. Ethylbenzene, as well as a variety of other hydrocarbons, has been implicated in the atmospheric formation of PAN in smog (Yanagihara et al. 1977).

The kinetics of partitioning and/or transformation processes are site-specific and depend upon many external factors. For example, the extent of biodegradation observed in an environmental medium depends upon the type and population of microorganisms present, the concentration of ethylbenzene, the

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



presence of other compounds that may act as a substrate, and the presence or absence of oxygen. Biodegradation in soil will also compete with transport processes such as volatilization and infiltration to groundwater. Because ethylbenzene migration is only moderately retarded by adsorption onto soil, leaching of the compound to an anaerobic environment (groundwater) before biotransformation in soil is possible and may allow ethylbenzene to persist in an aquifer.

Although information is limited on dietary exposures, ethylbenzene does not appear to significantly bioaccumulate in aquatic or terrestrial food chains, and human exposure through this route is not likely to be of concern.

Exposure of the general population to ethylbenzene is possible through contact with gasoline, automobile emissions, solvents, pesticides, printing ink, varnishes, coatings, and paints. Cigarette smoke also has been identified as a source of exposure to this chemical. Ethylbenzene is widely present at low concentrations in rural, suburban, and urban atmospheres with the highest concentrations generally detected in areas of gasoline stations, tunnels, highways, and parking lots. Ethylbenzene is also present in indoor air. Very often ethylbenzene levels in indoor air exceed the levels typically found in outdoor air (Dodson et al. 2008). Occupational exposures are expected within the petroleum industry; within industries using solvents, paints, and coatings; and during the manufacture and handling of ethylbenzene and styrene (which is manufactured from ethylbenzene).

Several groups within the general population may have potentially higher exposures to ethylbenzene by inhalation, oral, or dermal contact with contaminated drinking water or soil. These groups include individuals living near manufacturing and processing facilities, petroleum refineries, and hazardous waste disposal sites and those working or residing in high traffic areas. Exposures associated with the consumption of contaminated drinking water as well as with inhalation and dermal exposure during showering and bathing in contaminated water would be expected for individuals that derive their primary drinking water supply from residential wells downgradient of uncontrolled landfills, hazardous waste sites, and leaking underground storage tanks that are contaminated with ethylbenzene. Individuals living near these sites may also be exposed via dermal contact with, or ingestion of soil contaminated with ethylbenzene.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 4,586,441 pounds (~2,081 metric tons) of ethylbenzene to the atmosphere from 1,485 domestic manufacturing and processing facilities in 2006, accounted for about 82% 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 majority of ethylbenzene releases to the environment occur to the atmosphere. Because of its frequent use, and production in manufacturing operations, ethylbenzene is an important industrial chemical. Ethylbenzene is consistently ranked among the top 50 chemicals produced in the United States, with total production ranging from approximately 11 to 13 billion pounds annually (C&EN 1995, 2006; Kirschner 1995). In 2005, 11.6 billion pounds of ethylbenzene were produced by U.S. manufacturers (C&EN 2006). Its release can occur during manufacturing, processing, and handling. In 1978, emissions of ethylbenzene in the United States from catalytic reformate production alone were estimated at over 2 million pounds (Fishbein 1985). Ethylbenzene is also released to the air during processing of crude oil (Bratveit et al. 2007). Fuels and solvents, however, are considered to account for the bulk of emissions (Fishbein 1985). Exposure to ethylbenzene increases in areas high traffic areas (Smith et al. 2008). Ethylbenzene has been measured from tail pipe emissions of gasoline-powered vehicles at a weighted average rate of 12 mg/km (considering both catalyst and noncatalyst equipped cars) (Hampton et al.

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	11	4,790	9	0	374	0	5,168	5	5,173
AL	37	249,191	560	0	228	349	249,751	577	250,328
AR	17	63,827	5	0	78	0	63,833	77	63,910
AZ	19	33,661	12	0	0	0	33,673	0	33,673
CA	99	91,863	11	500	1,733	1,407	92,331	3,184	95,515
CO	10	2,435	0	0	10	0	2,435	10	2,445
CT	12	4,504	1	0	10	729	4,505	739	5,244
DE	3	7,175	0	0	1	0	7,175	1	7,176
FL	39	104,231	8	0	5	268	104,239	273	104,512
GA	33	80,852	1	0	229	1,742	80,853	1,971	82,824
GU	2	2,436	0	0	0	255	2,436	255	2,691
HI	10	3,312	53	0	170	78	3,365	248	3,613
IA	25	72,532	0	0	3	0	72,535	0	72,535
ID	2	111	No data	0	0	0	111	0	111
IL	69	173,154	170	0	1,300	1,449	173,355	2,718	176,073
IN	75	265,514	571	0	109	1,098	266,095	1,197	267,292
KS	19	71,934	96	14	22,148	0	86,545	7,647	94,192
KY	39	147,354	24	0	33,281	20,709	147,411	53,957	201,368
LA	68	272,307	935	170	3,774	0	273,286	3,900	277,187
MA	18	6,917	28	0	2,251	2,078	9,194	2,080	11,274
MD	20	13,195	5	0	1	0	13,200	1	13,201
ME	5	1,841	3	0	0	124	1,844	124	1,968
MI	66	363,099	3	0	12,317	574	363,107	12,886	375,993
MN	22	73,380	13	0	141	10	73,393	151	73,544
MO	48	214,512	1	0	45	246	214,513	291	214,804
MP	3	255	0	0	5	5	260	5	265
MS	21	171,586	33	0	0	0	171,619	0	171,619
MT	6	5,406	4	0	86	0	5,414	82	5,496
NC	25	31,809	0	0	4	807	31,811	809	32,620
ND	2	5,000	0	0	1	0	5,001	0	5,001
NE	8	2,830	0	0	54	0	2,855	29	2,884
NH	4	410	1	0	0	0	410	0	410
NJ	41	37,281	230	0	2,010	8	38,247	1,282	39,529
NM	8	10,585	5	5	186	1,334	10,772	1,343	12,115
NV	4	2,821	No data	0	0	0	2,821	0	2,821
NY	51	37,634	11	0	20	1,693	37,645	1,713	39,358
OH	99	289,303	303	0	2,618	701	290,754	2,171	292,925
OK	18	72,700	9	20	270	262	72,977	284	73,261

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Ethylbenzene[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
OR	16	35,640	1	0	0	3	35,641	3	35,644
PA	64	149,523	118	0	1,570	1,427	149,641	2,997	152,637
PR	10	15,209	10	0	5	47	15,224	47	15,271
RI	5	1,224	3	0	7	33	1,227	40	1,267
SC	17	48,768	55	31	52	4,565	48,823	4,648	53,471
SD	4	40,119	No data	0	0	0	40,119	0	40,119
TN	33	412,260	45	0	502	250	412,306	751	413,057
TX	158	627,282	1,625	843,929	13,835	2,262	1,462,679	26,254	1,488,933
UT	15	6,812	5	0	98	97	6,822	190	7,012
VA	25	66,825	99	0	180	79	66,924	259	67,183
VI	3	12,390	3	0	12	0	12,393	12	12,406
VT	1	608	No data	0	0	0	608	0	608
WA	19	30,388	11	0	169	36	30,536	68	30,605
WI	37	61,033	0	0	14	6,013	61,034	6,026	67,060
WV	14	75,811	9	0	15	398	75,820	413	76,233
WY	6	10,800	No data	0	261	0	10,805	256	11,061
Total	1,485	4,586,441	5,088	844,670	100,181	51,134	5,445,543	141,972	5,587,515

[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)

1983). Exposures to ethylbenzene can also occur while individuals are traveling in the passenger compartment of automobiles, and the chemical has been found at much higher concentrations during automobile engine malfunctions (Lawryk and Weisel 1996; Lawryk et al. 1995). Starting gasoline-powered vehicles in attached garages can contribute to increased indoor ethylbenzene exposure (Dodson et al. 2008). Emissions from gasoline-powered vehicles were found to be somewhat higher than from diesel trucks (Hampton et al. 1983). Similarly, ethylbenzene has been measured in jet fuel emissions (Katzman and Libby 1975) and has been reported in waste incinerator stack emissions (Jay and Steiglitz 1995; Junk and Ford 1980). Ethylbenzene has also been shown to be released into the atmosphere from volatile organic compound (VOC)-laden waste water in municipal sewer systems (Quigley and Corsi 1995).

Emissions of ethylbenzene can arise from transport of hot asphalt from a manufacturing plant to a paving site and from subsequent road paving operations. Kitto et al. (1997) measured the emissions of volatile organic compounds from Type I and Type II hot asphalts. At 150 °C, the concentration of the ethyl-benzene emissions from Type I asphalt was 800 μg/m^3; at 200 °C, the concentration was 2,200 μg/m^3, an increase by a factor of 2.8. At 150 °C, the concentration of the ethylbenzene emissions from Type II asphalt was 7,000 μg/m^3; at 200 °C, the concentration was 21,000 μg/m^3, an increase by a factor of 3.

Mukund et al. (1996) conducted chemical mass balance source apportionment modeling on a data set of 142 3-hour integrated air samples collected at six different sites in three separate campaigns during the summer of 1989 in Columbus, Ohio. The contributions (± standard error) to the observed atmospheric levels of ethylbenzene from the sources considered, expressed as percentage of measured average concentration, were: 55±11 from vehicle exhaust; 0.7±0.2 from gasoline vapor; 0±3 from natural gas; 20±4 from industrial solvents; and 0±1 from the dry cleaning/degreasing/waste water composite source. These five sources contributed an estimated 76±12% of the measured average concentration of 1.1 μg/m^3.

Ethylbenzene releases to the air especially in indoor environments can occur with the use of consumer products such as pesticides, liquid process photocopiers and plotters, solvents, carpet glue, paints, varnishes, automotive products, adhesives, and fabric and leather treatments that contain ethylbenzene (Hodgson et al. 1991; Lillo et al. 1990; NAS 1980; Otson et al. 1994; Sack et al. 1992; Wallace et al. 1987b). Indoor exposure to ethylbenzene may also result from the start-up of gasoline-powered engines in attached garages (Dodson et al. 2008). Ethylbenzene (in addition to other aromatic hydrocarbons, such as benzene, styrene, and xylenes) has also been measured in cigarette smoke (Barrefors and Petersson 1993; Wallace et al. 1986, 1987c). An analysis of indoor air in a home using gasoline-contaminated tap

water found that exposures to ethylbenzene could occur via inhalation during showering and other household activities (Beavers et al. 1996). Ethylbenzene concentrations in the shower area were often one to two orders of magnitude higher than in other areas of the home. Ethylbenzene has been identified in air samples collected at 121 of the 829 NPL hazardous waste sites respectively, where it was detected in some environmental media (HazDat 2007).

6.2.2 Water

Estimated releases of 5,088 pounds (~2.3 metric tons) of ethylbenzene to surface water from 1,485 domestic manufacturing and processing facilities in 2006, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional 141,972 pounds (~64.4 metric tons) were transferred off-site or released to publicly owned treatment works (POTWs) (TRI06 2008). These releases are summarized in Table 6-1.

Releases to water can occur as a result of industrial discharges (Snider and Manning 1982), fuel spillage (Gschwend et al. 1982; Tester and Harker 1981), leaking petroleum pipelines or underground storage tanks (Cotruvo 1985), landfill leachate (Barker 1987; Beavers et al. 1996; Chen and Zoltek 1995; Hallbourg et al. 1992), and the inappropriate disposal of wastes containing ethylbenzene (Eiceman et al. 1986). Ethylbenzene has been detected in both surface water and groundwater (EPA 2007i; Jin et al. 2007). Ethylbenzene emissions to oceans occur as a result of offshore oil production, hydrocarbon venting, oil field brines, and tanker oil spills (Sauer et al. 1978). Sauer and Tyler (1995) reported that ethylbenzene was one of the most commonly detected VOCs in motor vehicle waste fluids released from routine vehicle maintenance shops entering catch basins and septic tanks in Wisconsin. Ethylbenzene was detected at a mean concentration of 11 ppb (range 3–98 ppb) in catch basin waste water, 1.5 ppb (range 7–23 ppb) in septic tank effluent, and 8 ppb (range 9–53 ppb) in septic tank sludge.

Ethylbenzene has been identified in surface water at 123 sites and groundwater collected at 557 of the 829 NPL hazardous waste sites respectively, where it was detected in some environmental media (HazDat 2007).

6.2.3 Soil

Estimated releases of 100,181 pounds (~45.4 metric tons) of ethylbenzene to soils from 1,485 domestic manufacturing and processing facilities in 2006, accounted for about 2% of the estimated total environmental releases from facilities required to report to the TRI (TRI06 2008). An additional

844,670 pounds (~383.2 metric tons), constituting about 15% of the total environmental emissions, were released via underground injection (TRI06 2008). These releases are summarized in Table 6-1.

Ethylbenzene can be released to soils through the spilling of gasoline and other fuels (Sauer and Tyler 1995; Tester and Harker 1981); through the disposal of solvents and household products such as paint, cleaning and degreasing solvents, varnishes, and pesticides; through emissions from leaking underground or aboveground storage tanks, well pumping units, or pipelines(Cotruvo 1985; Soukup et al. 2007); and leaching from landfills or contaminated industrial sites (Barker 1987; Soukup et al. 2007).

Ethylbenzene has been identified in soil and sediment samples collected at 469 and 144 of the 829 NPL hazardous waste sites respectively, where it was detected in some environmental media (HazDat 2007).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The large vapor pressure and Henry's law constant of ethylbenzene (Table 4-2) suggests a moderate to strong tendency for ethylbenzene to partition into the atmosphere where it will exist predominantly in the vapor phase (Eisenreich et al. 1981; Mackay 1979; Masten et al. 1994). Depending upon site-specific conditions, releases to surface soil can result in substantial losses to the atmosphere in addition to subsurface infiltration. Since it has a moderately high vapor pressure, ethylbenzene will evaporate fairly rapidly from dry soil. Vapor phase transport will occur from subsurface releases (i.e., from leaking underground storage tanks) and during migration through unsaturated soil pore spaces (Rhue et al. 1988). Atmospheric reaction with hydroxyl radicals can limit the atmospheric transport of ethylbenzene (Dewulf and van Langenhove 1997).

The large Henry's law constant (Table 4-2), which measures partitioning between water and air, indicates that a significant proportion of ethylbenzene will partition from water into air (Mackay 1979; Masten et al. 1994). Ethylbenzene dissolved in surface water, soil pore water, or groundwater will thus migrate into an available atmospheric compartment until its saturated vapor concentration is reached. The volatilization half-life of ethylbenzene in a constructed wetland (length=228 m, width=60 m, depth=0.5–1.5 m) located in Phoenix, Arizona ranged from approximately 40 to 200 hours (Keefe et al. 2004).

Based on log K_{oc} values in the range of 2.2–2.4 (Table 4-2) and using the classification scheme of Swann et al. (1983), ethylbenzene is classified as having moderate mobility in soils. Sorption and retardation by

soil organic carbon content will occur to a moderate extent, but sorption is not significant enough to completely prevent migration in most soils. Particularly in soils with low organic carbon content, ethylbenzene will tend to leach into groundwater. Mobility is also possible in aquifers that contain very little solid-phase organic matter, a condition common to sand and gravel aquifers (Ptacek et al. 1984). Sorption and desorption experiments performed by Dewulf et al. (1996) demonstrated that the sorption process of ethylbenzene on marine sediments is reversible and that the sorption is even lower than expected from the log K_{ow} data and the organic carbon content of the sediment. They concluded that the marine sediment compartment is not an important sink for the VOCs investigated when they are released to water.

When ethylbenzene is part of a complex mixture of hydrocarbons associated with a petroleum spill or leak, the proportion of ethylbenzene that will bind to soil versus the amount that will migrate toward groundwater depends primarily on the type of soil, the biological environment in the soil, the particular petroleum product in which the ethylbenzene is dissolved, the size of the spill, and the amount of rainfall (Stokman 1987; Soukup et al. 2007). For example, the solubility of ethylbenzene varies in accordance with the presence of other petroleum products (Ptacek et al. 1984). While the pure compound solubility of ethylbenzene in water is 180 mg/L, its solubility in water equilibrated with JP-jet fuel is 10.6 mg/L (Burris and MacIntyre 1984). Potter (1993) also reported that the equilibrium aqueous solubility of ethylbenzene was 2.4 mg/L with gasoline, 0.18 mg/L with diesel fuel, and 0.007 mg/L with #6 fuel oil equilibrated with groundwater. Both of these authors calculated the solubility concentrations of ethylbenzene in water equilibrated with various petroleum products. In addition, solvent spills of chemicals such as ethylbenzene may enhance the mobility of other organic chemicals, which do strongly adsorb to soil (Rao et al. 1985). No information was found concerning bioavailability of ethylbenzene from soil for human dermal or oral uptake.

Boyd et al. (1990) reported that corn residues high in organic matter that were left on the surface of a no tillage field, adsorbed a significantly greater amount of ethylbenzene as compared with surface soil. The authors suggested that the highly lipophilic plant cuticle appears to be the sorptive component. Kango and Quinn (1989) also reported that humic acid adsorbed higher amounts of ethylbenzene and xylenes ranging from 40 to 77 times greater than soil.

Once in the atmosphere, ethylbenzene will be transported until it is removed by physical or chemical processes. Physical removal processes, which involve partitioning into clouds or rainwater, are relevant to ethylbenzene, which has been measured in Los Angeles rainwater (Kawamura and Kaplan 1983). The

concentrations of several dissolved organic chemicals in rainwater and in the atmosphere during rainfall events were measured by Ligocki et al. (1985). The authors found that the concentration of ethylbenzene in rain water was approximately equal to the inverse of the dimensionless Henry's law constant (Table 4-2) at atmospheric temperatures. This indicates that ethylbenzene is removed from the atmosphere through precipitation, but it can re-enter the atmospheric environment upon evaporation.

In comparison to chemicals such as polychlorinated biphenyls (PCBs), DDT, and other chlorinated pesticides, which are of great concern with respect to bioaccumulation, ethylbenzene does not significantly bioaccumulate in aquatic food chains. A measured bioconcentration factor (BCF) of 15 was reported for ethylbenzene in goldfish (Ogata et al. 1984). A BCF value of 53 was estimated in fish, using a log K_{ow} of 3.15 and a regression derived equation (Meylan et al. 1999). A 3% weighted average lipid content in fish and shellfish was assumed by EPA in the calculation. The calculated BCF is a theoretical value based on known constants, and is a conservative estimate of the bioconcentration of this chemical in fish. A calculated BCF of 167 was also estimated for fathead minnows (*Pimephales promelas)* (ASTER 1995). In a shellfish study, the ethylbenzene concentration in clam tissue was 5 times higher than that measured in water after an 8-day continuous-flow exposure to the water-soluble fraction of Cook Inlet crude oil (Nunes and Benville 1979).

Ethylbenzene has also been found to partition into human tissues; primarily as a result of inhalation exposures (see Section 6.5). Ethylbenzene has been detected in human adipose tissue (Sections 3.4.2.1 and 3.8.1), blood (Section 3.4.1.1), and in breast milk (Section 3.7). No information was located concerning the bioavailability of ethylbenzene from contaminated soil or sediment either with respect to dermal exposure or oral intake via consumption of soil particles from unwashed hands.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Ethylbenzene undergoes atmospheric transformations through reaction with photochemically generated hydroxyl radicals (Atkinson et al. 1978; Ohta and Ohyama 1985; Ravishankara et al. 1978), NO_3 radicals (Atkinson et al. 1987), and atomic oxygen (Grovenstein and Mosher 1970; Herron and Huie 1973). Gas phase reactions with ozone and structurally similar molecules such as toluene have been observed (Atkinson and Carter 1984). The predominant degradation pathway for ethylbenzene in the atmosphere occurs via reaction with hydroxyl radicals and nitrate radicals (which are only present during non daylight hours), with the other degradation mechanisms being of only minor importance. The rate constant for the

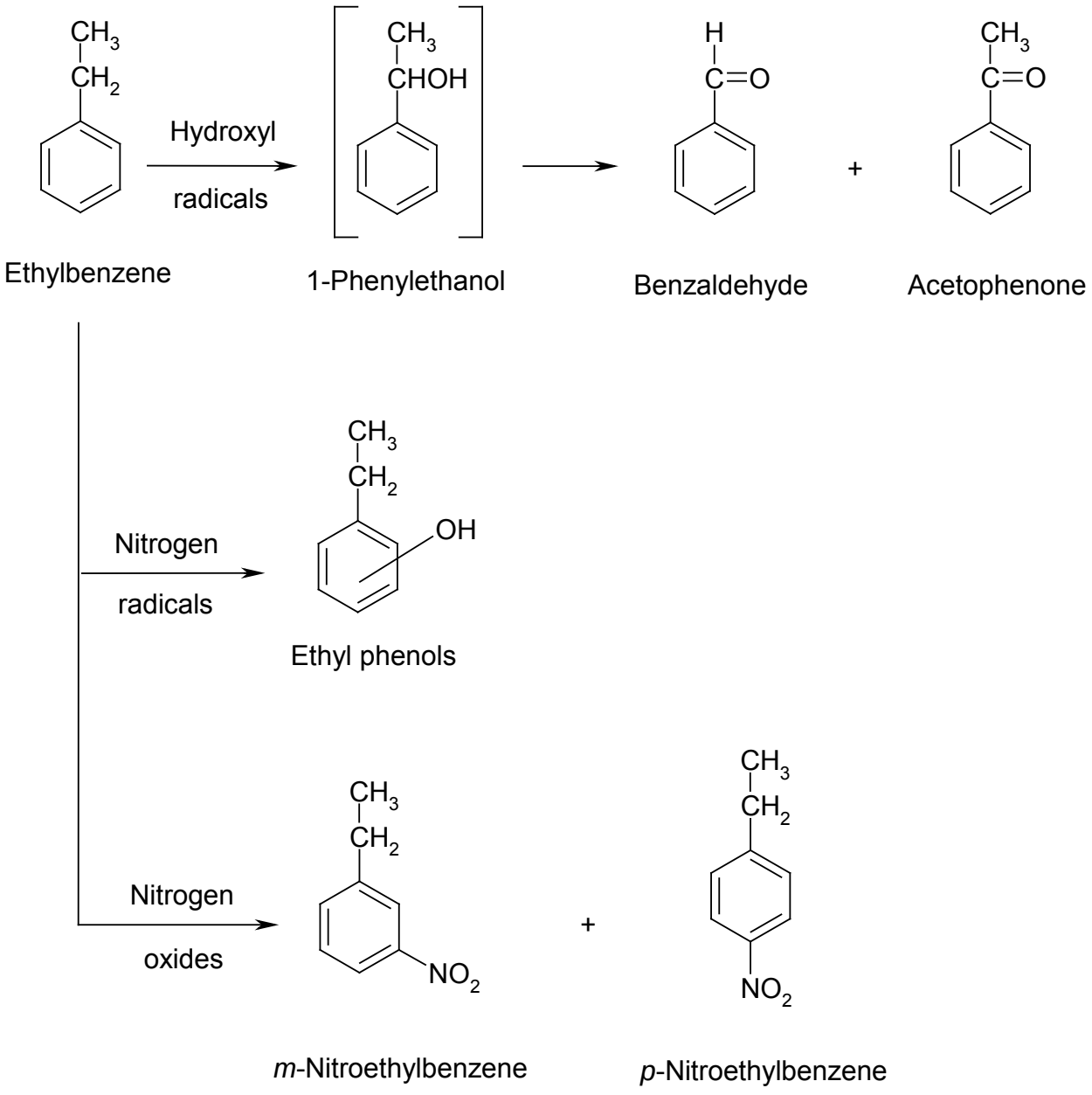
vapor phase reaction of ethylbenzene with photochemically generated hydroxyl radicals was measured as $7.1x10^{-12}$ cm^3 per molecule-second (Kwok and Atkinson 1994). This corresponds to an atmospheric half-life of approximately 2 days using a hydroxyl radical concentration of $5x10^5$ hydroxyl radicals per cm^3. The rate constant for the degradation of ethylbenzene with nitrate radicals was measured as $6x10^{-16}$ cm^3 per molecule-second (Atkinson et al. 1987). Using a nighttime nitrate radical concentration of $5x10^8$ nitrate radicals per cm^3, a half-life of approximately 26 days is estimated. Atmospheric degradation occurs more rapidly during summer months as opposed to winter since the concentration of hydroxyl radicals in the atmosphere peaks during summer (Ravishankara et al. 1978; Singh et al. 1981), and is also faster under photochemical smog conditions (Dilling et al. 1976). Oxidation by-products from the reaction with hydroxyl radicals and nitrogen oxides include ethylphenols, benzaldehyde, acetophenone, and *m*- and *p*-nitroethylbenzene (Hoshino et al. 1978). The major degradation pathways for ethylbenzene in the atmosphere are summarized in Figure 6-2.

Experiments conducted with various hydrocarbons on the formation of photochemical aerosols or the haze associated with smog revealed that aromatics such as ethylbenzene produced only low yields of aerosol when compared with more reactive compounds such as alkenes (O'Brien et al. 1975). The formation of PAN is related to the photoreactivity of the reacting hydrocarbon. The photoreactivity of ethylbenzene is intermediate relative to other atmospheric hydrocarbons, and it is less reactive than gasoline, toluene, and alkenes such as propene (Yanagihara et al. 1977).

6.3.2.2 Water

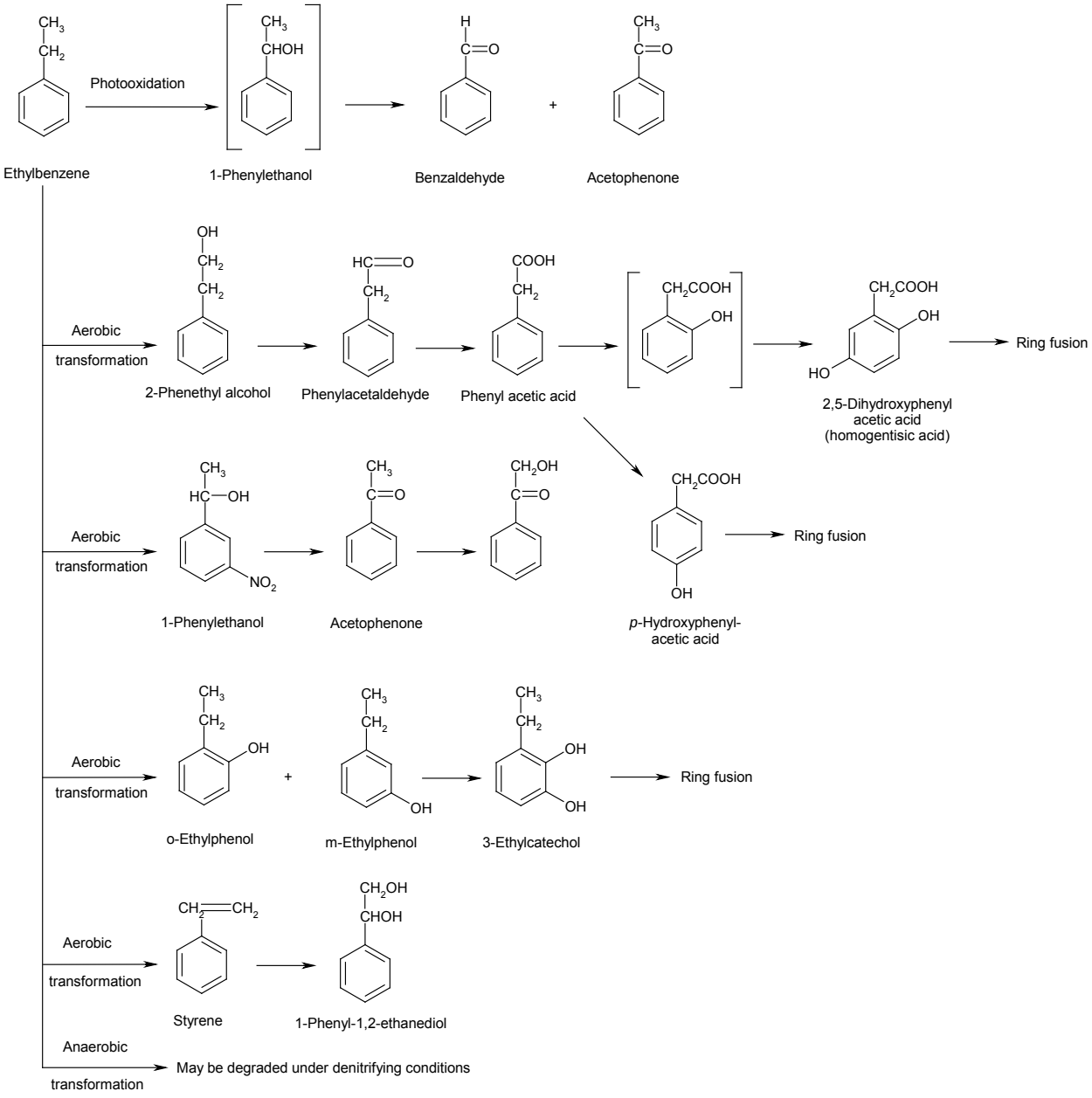
In surface water, transformations of ethylbenzene may occur through two primary processes—photooxidation and biodegradation. Since ethylbenzene does not contain hydrolysable functional groups at environmental pH (pH 5–9), hydrolysis is not considered an important environmental fate process. Although ethylbenzene does not absorb light in the environmental ultraviolet spectrum, it is capable of undergoing photooxidation in water through an indirect reaction with other light-absorbing molecules, a process known as sensitized photolysis. The compounds 1-methylphenyl ketone (acetophenone), 1-phenylethanol, and benzaldehyde were identified as degradation products from the laboratory photooxidation of ethylbenzene in both distilled water and seawater with anthraquinone used as a sensitizer (Ehrhardt and Petrick 1984). In the environment, similar degradation is expected to occur in the presence of ubiquitous, naturally occurring humic material sensitizers. The major degradation pathways for ethylbenzene in water are summarized in Figure 6-3.

Figure 6-2. Major Degradation Pathways for Ethylbenzene in the Atmosphere



Source: Hoshino et al. 1978

Figure 6-3. Major Degradation Pathways for Ethylbenzene in Water, Sediment, and Soil



Source: Burback and Perry 1993; Ehrhardt and Petrick 1984; Van der Linden and Thijsse 1965

Biodegradation in aerobic surface water will compete with sensitized photolysis and transport processes such as volatilization. Volatilization and biodegradation of ethylbenzene in seawater have been observed by Gschwend et al. (1982), Masten et al. (1994), and Wakeham et al. (1983). Migration from surface water to subsurface soil with low amounts of oxygen or to aquifers with lower microbial populations, however, will limit the rate of transformation. No significant disappearance of ethylbenzene during 11 weeks of incubation with bacteria under low oxygen (anoxic) conditions was observed by Bouwer and McCarty (1983). Slow degradation of ethylbenzene was reported in anaerobic aquifer materials known to support methanogenesis, although a long acclimation period or lag time was required (Wilson et al. 1986). Less than 1% of the initial concentration of ethylbenzene remained after 120 weeks, indicating that, given sufficient time, ethylbenzene will be essentially completely biodegraded.

Laboratory microcosm tests were conducted to determine optimum conditions for ethylbenzene biodegradation by aquifer microorganisms under denitrifying condition (Hutchins 1991). Ethylbenzene was degraded to <5 µg/L when present as a sole source substrate and stoichiometric calculations indicated that nitrate removal was sufficient to account for 70–80% of the compound being mineralized. Biodegradation did not occur without the presence of nitrate, and nitrate removal was minimal without the presence of the ethylbenzene over a 55-day incubation period. In a laboratory microcosm containing aquifer material and groundwater from the North Bay site in Ontario, Canada, no significant loss of ethylbenzene was observed compared to unamended controls over a period of 187 days. In another experiment conducted at the North Bay site that used *in situ* biodegradation columns, ethylbenzene was completely degraded in at least 1 of the 8 *in situ* columns in <100 days (Acton and Barker 1992). In all cases, the authors attributed the ethylbenzene attenuation to biodegradation by methanogenic and fermentative bacteria. In another study using a laboratory scale flow-through aquifer column system, low dissolved oxygen (<1 mg/L) conditions were initiated with the nitrate-amended column influent in order to mimic contaminated groundwater conditions distal from a nutrient injection well (Anid et al. 1993). The authors reported that 40% of the ethylbenzene was removed after several months of operation. In a similar study, using batch incubations seeded with four different aquifer materials, ethylbenzene was not degraded within 4 months in any of the denitrifying enrichments tested, even though nitrate reduction occurred. Burback and Perry (1993) reported than *Mycobacterium vaccae* can catabolize a number of major groundwater pollutants, including ethylbenzene. At a concentration of 100 ppm, ethylbenzene was not measurably degraded; however, at 50 ppm, 80% of the added ethylbenzene was degraded. A product peak of 4-ethylphenol was detected as well as a small amount of 1-phenylethanol.

The contrast between biodegradation rates in the presence or absence of oxygen was demonstrated by a biofilm reactor study designed to simulate an aquifer (Bouwer and McCarty 1984). Continuous-flow laboratory column studies under aerobic and methanogenic conditions were performed with mixed bacterial cultures on glass beads. In the aerobic biofilm column, 99% of the ethylbenzene initially present was degraded within a 20-minute detention time, while under methanogenic (anaerobic) conditions, only 7% was degraded within a 2-day detention time.

6.3.2.3 Sediment and Soil

Biodegradation of ethylbenzene by aerobic soil microbes has been reported by various researchers. The common soil microorganism *Pseudomonas putida* is able to utilize ethylbenzene as a sole source of carbon and energy (Fukuda et al. 1989; Gibson et al. 1973). In some instances, co-oxidation or co-metabolism was observed (i.e., ethylbenzene was degraded by *Nocardia sp.* in the presence of other compounds that are more readily metabolized by the microorganism) (Jamison et al. 1970; Van der Linden and Thijsse 1965). Yadav and Reddy (1993) reported that the white-rot fungus *Phanerochaete chrysosporium* efficiently degraded ethylbenzene as well as other benzene, toluene, ethylbenzene, and xylenes (BTEX) compounds when these chemicals were added either individually or as a composite mixture. In addition, substantially greater degradation of all the BTEX compounds was observed in static rather than in shaken liquid cultures. Furthermore, degradation was greater at 25 °C than at 37 °C, but pH variations between 4.5 and 7 had little effect on the extent of the degradation. Chen and Taylor (1995) reported that two thermophilic bacterial strains, *Thermus aquaticus* and an unidentified *Thermus sp*. degraded ethylbenzene (in a mixture with other BTEX chemicals) by 18% after 45 days of incubation at 70 °C and by 32% after 45 days of incubation at 60 °C, respectively. Zappi et al. (1996) reported that ethylbenzene degraded rapidly in a pilot scale bioslurry reactor under aerobic conditions. The initial concentration (0.35 mg/kg) was degraded by 94% in 2 days.

Biotic transformations by aerobic soil microbes involve oxidation of the ethyl side chain to form phenylacetic acid (Van der Linden and Thijsse 1965) and 1-phenylethanol (Bestetti and Galli 1984); ring hydroxylation to form 2,3-dihydroxy-1-ethylbenzene (Gibson et al. 1973), 2-hydroxyphenlacetic acid, 4-hydroxyphenylacetic acid, and 2,5- and 3,4-dihydroxyphenylacetic acid (Van der Linden and Thijsse 1965); and ultimate ring cleavage to form straight chain carboxylic acids such as fumaric and acetoacetic acids (Van der Linden and Thijsse 1965). The major degradation pathways for ethylbenzene are summarized in Figure 6-3.

Anaerobic degradation of ethylbenzene based on observations from studies conducted under anaerobic conditions in other media and as discussed above (Bouwer and McCarty 1983, 1984; Wilson et al. 1986), would be much slower than that observed under aerobic conditions. Ramanand et al. (1995) studied the biodegradation of several organic pollutants including ethylbenzene in soil columns under denitrifying conditions. These authors reported that one of the significant factors governing biodegradation is the availability of suitable electron acceptors. The biodegradation of ethylbenzene, toluene, and xylenes has been demonstrated in laboratory samples obtained from subsurface habitats or in pure cultures under dinitrifying conditions (Hutchins 1991; Hutchins et al. 1991). Ramanand et al. (1995) reported that soil column bacteria, after sufficient acclimation time, metabolized 100–500 μM of toluene and ethylbenzene in <6 days under denitrifying conditions. These compounds were successfully degraded under anoxic conditions by the addition of nitrate and by stimulating the indigenous soil denitrifying bacteria.

The kinetics of biodegradation appear to be site specific, and depend upon factors such as the type and population of microbes present, the environmental temperature, the concentration of ethylbenzene, the presence of other compounds that may act as a substrate, and the amount of oxygen and electron acceptors present. Biodegradation in soil will also compete with migration processes such as volatilization and infiltration to groundwater.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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

6.4.1 Air

Ambient air levels of volatile organic compounds, including ethylbenzene, were monitored as a part of a multi-media study known as the Lower Rio Grande Valley Environmental Scoping Study. Monitoring was performed at a “central” site and at a “border” site in the Brownsville, Texas, air shed in the spring and summer of 1993. The median ambient concentration of ethylbenzene at the central site was 0.80 μg/m^3 (0.18 ppbv) (n=22; range=0.20–1.7 μg/m^3 [0.046–0.39 ppbv]) in the spring and 0.4 μg/m^3

(0.09 ppb) (n=14; range=0.2–1.0 μg/m^3 [0.04–0.2 ppbv]) in the summer. These concentrations are either lower or comparable to those found in previous EPA and other monitoring investigations (Ellenson et al. 1997). The median indoor concentration of ethylbenzene for nine Rio Grande Valley residences measured in the spring was 1.00 μg/m^3 (0.230 ppbv) compared to a median outdoor concentration of 0.70 μg/m^3 (0.16 ppbv); in the summer, the median indoor concentration of ethylbenzene for five residences was 1.40 μg/m^3 (0.321 ppbv) compared to a median outdoor concentration of 0.35 μg/m^3 (0.080 ppbv) (Mukerjee et al. 1997). The mean indoor concentration of ethylbenzene at the homes of 46 high school students residing in New York City was 3.57 μg/m^3 (0.821 ppbv) in the winter months as compared to a mean indoor concentration of 1.99 μg/m^3 (0.458 ppbv) during the summer months (Kinney et al. 2002). The corresponding mean outdoor levels of ethylbenzene were 1.27 (0.292 ppbv) and 1.88 μg/m^3 (0.432 ppbv) in the winter and summer months, respectively.

An update of the 1980 National Ambient Volatile Organic Compounds (VOC) database prepared for EPA summarized concentrations of ethylbenzene by site type (EPA 1988c). Median values are reported because they are less biased by a few high or low concentrations and, thus, may better represent the data than would average values. The median indoor concentration of ethylbenzene detected at 95 locations was 1.0 ppbv (4.4 μg/m^3) (mean 2.9 ppbv), while personal air monitoring of 1,650 individuals found a median concentration of 1.3 ppbv (5.6 μg/m^3) (mean 3.2 ppbv).

Of particular interest is that personal air monitoring of indoor air found higher concentrations of ethylbenzene than those observed in outdoor air. This was also observed during the Total Exposure Assessment Methodology (TEAM) Study conducted by EPA between 1979 and 1985 in an effort to measure exposures to 20 VOCs in personal air, outdoor air, and drinking water. The major cause for the higher personal air concentrations was felt to be the presence of ethylbenzene sources in the home. In the TEAM study, tobacco smoke was reported to be a main source of exposure to volatile aromatic compounds such as ethylbenzene (Wallace et al. 1987a, 1987c). Based on the results of a stepwise regression carried out on data collected during the fall in New Jersey from 352 participants, overnight geometric mean ethylbenzene exposures of persons living in homes with smokers were approximately 1.5 times the geometric mean exposures of persons living in homes without smokers. The amount of ethylbenzene measured in mainstream smoke of a single cigarette containing 16 mg of tar and nicotine was 8 μg (Wallace et al. 1987c). Wallace et al. (1989) reported that a maximum outdoor air concentration of ethylbenzene of 7.4 μg/m^3 (1.7 ppbv) was detected in nine outdoor samples collected at each of three houses while maximum indoor air concentrations at these same residences ranged from 5 to 110 μg/m^3

(1–25.3 ppbv). Mean personal exposures averaged 28 μg/m^3 (6.4 ppbv) (range 4.6–144 μg/m^3 [1.0–33.1 ppbv]) and the personal/outdoor ratio for ethylbenzene was 16.

The poor quality of indoor air has been linked to a number of symptoms (headache; nausea; irritation of the eyes, mucous membranes, and respiratory system; drowsiness; fatigue; and general malaise) which have been defined as "sick building" syndrome. Kostiainen (1995) identified over 200 VOCs in the indoor air of 26 normal houses. Ethylbenzene was detected in 100% of the houses studied at an average concentration of 3.2 μg/m^3 [0.74 ppbv] (median 2.41 μg/m^3 [0.554 ppbv], minimum 0.62 μg/m^3 [0.14 ppbv], and maximum 10.54 μg/m^3 [2.42 ppbv] concentration). The median concentration of ethylbenzene (2.41 μg/m^3 [0.554 ppbv]) in these normal houses was lower in all but one case than ethylbenzene concentrations detected in houses with "sick building" syndrome where the concentrations ranged from 2.25 to 747.24 μg/m^3 (0.517–172 ppbv).

A nationwide study of indoor air concentration of 26 VOCs was conducted in Canada in 1991 (Fellin and Otson 1994). These authors reported that mean indoor ethylbenzene concentrations were 6.46 μg/m^3 (1.48 ppbv), 8.15 μg/m^3 (1.87 ppbv), 4.35 μg/m^3 (1.00 ppbv) , and 13.98 μg/m^3 (3.21 ppbv) in the winter, spring, summer and fall months, respectively and that the concentrations declined with an increase in ambient air temperature. At ≤0, 0–15, and ≥15 °C, the mean ethylbenzene concentrations were 12.76 μg/m^3 (2.93 ppbv), 7.78 μg/m^3 (1.79 ppbv), and 6.46 μg/m^3 (1.48 ppbv), respectively. These authors concluded that indoor sources of ethylbenzene (primarily from household products) are likely to have a more significant influence on indoor air concentrations than climatic variables.

Concentrations of ethylbenzene were measured in soil gas, and indoor and outdoor air of a home located near a landfill in California (Hodgson et al. 1992). During the first sampling in September, ethylbenzene concentrations were not detected in soil gas or outdoor air, but were detected at 0.6 ppbv (3 μg/m^3) in basement air. In October, ethylbenzene concentrations averaged 3.3 ppbv (14 μg/m^3) in soil gas, 0.8 ppbv (4 μg/m^3) in basement air, and 0.7 ppbv (3 μg/m^3) in bedroom air. In this study, the authors found that the existence of soil gas contamination alone is not sufficient to result in significantly elevated indoor exposures. The entry rate of ethylbenzene and VOCs form the soil into the house was low. The limited entry that occurred at the conditions of the study was apparently the result of diffusive and advective flux of VOC through the cement blocks used in the basement wall construction. The authors suggest that there is a general need to identify variables associated with residential sites with the highest potential for significantly elevated indoor exposures resulting from soil gas contamination.

Indoor VOC concentrations were analyzed in 12 California office buildings as part of the California Healthy Building Study (Daisey et al. 1994). These authors reported that ethylbenzene was detected at a geometric mean of 0.50 μg/m^3 (0.11 ppbv) (range 0.27–0.98 μg/m^3 [0.062–0.22 ppbv]). These authors also reported that an estimated 82% of indoor air concentrations were contributed from motor vehicle emissions. Hodgson et al. (1991) reported that concentrations of ethylbenzene in indoor air of a new office building ranged from 7 to 18.7 μg/m^3 (2–4.30 ppbv) over the course of a 14-month sampling period. Furthermore, ethylbenzene indoor air concentrations were higher than those in outdoor air and that the dominant source of VOCs in the building was liquid-process photocopiers and plotters which emitted a characteristic mixture of C_{10}–C_{11} isoparaffinic hydrocarbons.

VOC concentrations were monitored both indoors and outdoors, including garages, basements, and common spaces, for 55 Boston area residences as part of the Boston Exposure Assessment in Microenvironmental (BEAM) study. Indoor and outdoor arithmetic mean ethylbenzene concentrations of 2.4 and 0.42 μg/m^3, respectively, were reported. Arithmetic mean ethylbenzene concentrations in garages, basements, and common hallways were 35, 4.1, and 2.1 μg/m^3, respectively. VOC concentrations also varied seasonally, tending to be higher in summer than winter (arithmetic mean ethylbenzene concentrations of 0.06 and 0.04 μg/m^3, respectively). Attached garages attributed to approximately 20–40% of gasoline-associated indoor VOC concentrations, while basements contributed approximately 10–20% and common hallways contributed 5–10% of indoor concentrations (Dodson et al. 2008).

Wadden et al. (1995) reported average VOC concentrations for indoor air monitored in a sheetfed offset printing shop. These authors reported mean ethylbenzene concentrations ranging from 0.27 to 0.84 mg/m^3 (0.062–0.19 ppmv) based on 12 1-hour samples.

Levels of ethylbenzene monitored in ambient air show great variation (Jonsson et al. 1985). Generally, air concentrations are much lower in rural areas than in urban areas, where vehicle emissions are thought to be a major contributor of ethylbenzene to ambient air. Ethylbenzene concentrations range from below detection limits in rural areas to 100 μg/m^3 (23.0 ppbv) on busy urban streets (Jonsson et al. 1985). Kelly et al. (1994) reported a median concentration of ethylbenzene of 1.1 μg/m^3 (0.25 ppbv) for 8,723 samples collected from 93 locations throughout the United States.

Ambient air concentrations reported for Deer Park, Texas suggest a correlation between high traffic areas and VOC concentrations. The mean ethylbenzene concentration for 12 sites was 0.51 μg/m^3 (0.12 ppbv).

High correlations between toluene, ethylbenzene, and xylenes suggest petroleum-related sources (Smith et al. 2008).

Median outdoor air concentrations of ethylbenzene for 6 remote and 122 rural locations are reported as 0.156 and 0.013 ppbv (0.679 and 0.056 μg/m^3), respectively (EPA 1988c). Median concentrations of 0.62 ppbv (2.7 μg/m^3) were reported for 886 suburban and 1,532 urban locations. The daily median concentration of ethylbenzene considering all site types including source dominated areas and workplace air was 0.60 ppbv (2.6 μg/m^3). Table 6-2 lists some monitoring results reported for ethylbenzene in various cities.

Ethylbenzene concentrations at four locations along U.S. Highway 70 near Raleigh, North Carolina, during the month of May were reported to range from 10 to 16 ppbv (44–70 μg/m^3) that were corrected to include upwind concentrations (Zweidinger et al. 1988).

Concentrations of ethylbenzene were measured in two tunnels: the Fort McHenry Tunnel in Baltimore, Maryland (June 18–24, 1992) and the Tuscarora Mountain Tunnel in Pennsylvania (September 2–8, 1992) (Zielinska et al. 1996). These authors reported minimum and maximum ethylbenzene concentrations (on a carbon basis) for the Fort McHenry Tunnel of 6.3 and 89.2 ppbC (0.79 and 11.2 ppbv) for bore #3, respectively, and 0.5 and 114.1 ppbC (0.06 and 14.26 ppbv) for bore #4, respectively, and concentrations for the Tuscarora Tunnel of 1.2 and 11.1 ppbC (0.15 and 6.04 ppbv) , respectively. The total number of light-duty vehicles (LDV) and heavy-duty vehicles (HDV) that passed through each tunnel was 12,273 LDV and 187 HDV for bore #3 and 11,788 LDV and 2,417 HDV for bore #4 of the Fort McHenry Tunnel and 4,887 LDV and 1,041 HDV for the Tuscarora Tunnel.

Ethylbenzene is released during processing of crude oil. Bratveit et al. (2007) reported air concentrations ranging from an average of 0.01–0.09 ppm of ethylbenzene over a 12-hour period, with individual measurements reported as high as 1.11 ppm (Bratveit et al. 2007).

Ethylbenzene and other VOCs have been found to be removed from waste water in municipal sewers and were emitted to the ambient atmosphere prior to entering a downstream waste water treatment facility in Toronto, Ontario (Quigley and Corsi 1995). These authors measured concentrations of ethylbenzene during four monitoring events and found that concentrations ranged from not detectable to 5 ppm. Headspace concentrations of ethylbenzene exhibited a significant weekday/weekend trend. Significant emissions of all VOCs monitored occurred during three of the four monitoring events. Ethylbenzene had

Table 6-2. Ethylbenzene Concentrations in Ambient Air Samples Collected in the United States

Location	Concentration	Comments	Reference
Downey, California	4.6±3.7 ppb (mean±SD) 16.1 ppb[a]	February 18–27, 1984; n=100	Singh et al. 1985
Los Angeles, California	3–12 ppb (range)	September 29–November 13, 1981	Grosjean and Fung 1984
Riverside, California	1.3±0.8 ppb (mean±SD) 4.0 ppb[a]	July 1–13, 1980; n=100	Singh et al. 1985
Denver, Colorado	2.2±3.1 ppb (mean±SD) 18.5 ppb[a]	June 15–28, 1980; n=100	Singh et al. 1985
Chicago, Illinois	0.8±1.2 ppb (mean±SD) 9.5 ppb[a]	April 20–May 2, 1981; n=100	Singh et al. 1985
St. Louis, Missouri	0.6±0.5 ppb (mean±SD) 2.1 ppb[a]	May 29–June 9, 1980; n=100	Singh et al. 1985
Camden, New Jersey	0.17 ppb (mean)	July 6–August 16, 1981; n=35	Harkov et al. 1983
Elizabeth, New Jersey	0.26 ppb (mean)	July 6–August 16, 1981; n=37	Harkov et al. 1983
Newark, New Jersey	0.33 ppb (mean)	July 6–August 16, 1981; n=38	Harkov et al. 1983
Staten Island, New York	1.7±2.5 ppb (mean±SD) 17.2 ppb[a]	March 26–April 5, 1981; n=100	Singh et al. 1985
Staten Island, New York	2.7±4.2 ppb (mean±SD) 16.7 ppb[a]	April 25–May 1, 1984; n=100	Singh et al. 1985
Philadelphia, Pennsylvania	0.8±0.8 ppb (mean±SD) 7.3 ppb[a]	April 4–22, 1983 n=100	Singh et al. 1985
Pittsburgh, Pennsylvania	0.8±1.6 ppb (mean±SD) 10.5 ppb[a]	April 7–17, 1981; n=100	Singh et al. 1985
Houston, Texas	1.5±1.6 ppb (mean±SD) 8.2 ppb[a]	March 8–17, 1984; n=100	Singh et al. 1985
Jones State Forest, Texas	2.8 ppb[b]	January 4–6, 1978	EPA 1979

[a]Maximum measured concentration
[b]Median concentration in 10 bag samples (median concentration in 5 can samples was 1.0 ppb)

n = number of samples; SD = standard deviation

the second highest emissions during all periods and ranged from 7 to 14 g/hour (62–130 kg/year) for event 1 and from 1 to 13 g/hour (9–115 kg/year) for event 2. Ethylbenzene emissions at five municipal treatment facilities ranged from 0.08 to 93 g/day (0.003–3.9 g/hour). Results of this study suggest that sewers that accept VOC-laden waste water, and that are characterized by significant ventilation and drop structures, can be significant sources of VOC emissions (including ethylbenzene) relative to municipal waste water treatment facilities.

Assmuth and Kalevi (1992) reported that ethylbenzene was detected in municipal solid waste landfill gas at minimum and maximum concentrations of 6.6–7.6 mg/m^3 (1.5–1.7 ppmv), <0.1–9.6 mg/m^3 (<0.02–2.2 ppmv), 0.2–1.2 mg/m^3 (0.04–0.28 ppmv), and 85–98 mg/m^3 (20–22 ppmv) at four different landfill sites in Finland. Concentrations of ethylbenzene measured in a biogas collection system at the Miron Quarry Municipal Waste Landfill Site in Montreal, Quebec ranged from 2 to 36 mg/m^3 (0.5–8.3 ppmv) (Goldberg et al. 1995).

6.4.2 Water

The median ethylbenzene concentration in ambient surface waters in the United States in 1980–1982 was <5.0 µg/L (ppb) according to EPA's STORET water quality database (Staples et al. 1985). The chemical was detected in 10% of the 1,101 samples collected during that period. Ethylbenzene was also detected in 7.4% of the 1,368 industrial effluent samples collected during 1980–1982 at a median concentration of <3.0 µg/L (ppb). More recent data from the STORET database indicated that ethylbenzene was only detected in 15 out of 548 surface water samples obtained from January 2005 to March 2007, at a maximum concentration of 2 ppb (EPA 2007i).

From 1989 to 1993, New York City municipal waste waters were analyzed to determine the frequency of detection of organic priority pollutants, including ethylbenzene (Stubin et al. 1996). Ethylbenzene was detected in 14 of 84 (17%) influent samples at concentrations ranging from 1 to 11 µg/L (ppb) and in only 1 of 84 (1%) effluent samples at a concentration of 2 µg/L (ppb).

Ethylbenzene and other VOCs have been detected in waste water in municipal sewers prior to entering a downstream waste water treatment facility in Toronto, Ontario (Quigley and Corsi 1995). These authors measured concentrations of ethylbenzene in waste water during several monitoring events and found that concentrations ranged from 0.059 to 0.086 mg/L (ppm) in one event and from 7 to 11 mg/L (ppm) in another event. The authors also determined that the stripping efficiency across two drop structures with

waste water fall heights of 1.4–3 meters within the sewer system removed 31–36% of the ethylbenzene in the waste water. Results of this study suggest that sewers that accept VOC-laden waste water, and that are characterized by significant ventilation and drop structures, can be significant sources of VOC emissions (including ethylbenzene) relative to municipal waste water treatment facilities.

As part of EPA's Nationwide Urban Runoff Program, ethylbenzene was measured in 4% of the municipal runoff samples collected in 15 cities throughout the United States (Cole et al. 1984). The measured ethylbenzene concentration range was 1–2 µg/L (ppb). Ethylbenzene was detected in 41 out of 249 (16.5%) storm water runoff samples collected at 46 different sampling locations in North Carolina over a 1-year period (Borden et al. 2002). The mean, median, and maximum ethylbenzene levels were 0.10, 0.07, and 0.36 µg/L (ppb), respectively.

Ethylbenzene was measured in seawater at an average concentration of 0.011 µg/L (ppb) and a concentration range of 0.0018–0.022 µg/L (ppb) over a 15-month observation period at Vineyard Sound, Massachusetts (Gschwend et al. 1982). Ethylbenzene also has been reported in surface waters of the Gulf of Mexico at a concentration range of 0.0004–0.0045 µg/L (ppb) (Sauer et al. 1978).

Ethylbenzene has been detected in a relatively remote location (Mt. Mitchell, North Carolina) in cloud water at a mean concentration of 170 ng/L (range 0–450 ng/L) (Aneja 1993). The average concentration of ethylbenzene in precipitation was 34 ng/L. Ethylbenzene has also been detected in snow samples from two remote sites in the province of Québec, Canada (Kos and Ariya 2006). Ethylbenzene levels reported in µg/L±3σ were: 2.65±1.28 (Resolute Bay); 0.22±0.02 (Gaspé Peninsula); and 0.31±0.06 (Gaspé Peninsula).

From 1989 to 1990 and from 1992 to 1993, ethylbenzene was monitored in wetland-treated leachate water at a municipal solid waste landfill in central Florida (Chen and Zoltek 1995). During the first sampling period, ethylbenzene was detected in surface water samples ranging from 0.06 to 0.09 ppb and in groundwater samples ranging from 0.06 to 9.75 ppb. During the second sampling period (1992–1993), ethylbenzene was not detected in surface water samples, but was detected in groundwater samples at concentrations ranging from below detection limits to 10.55 ppb. Ethylbenzene was detected in a study of three landfills in central Florida (Hallbourg et al. 1992). These authors reported concentrations of ethylbenzene in groundwater of 1.63–9.75, <1–83.8, and <1–8.6 µg/L (ppb) at the three different landfill sites. The mean concentration of ethylbenzene detected in landfill leachate from these disposal areas was 17.5 µg/L.

Ethylbenzene was measured in all three drinking water plants sampled as part of the New Orleans Area Water Supply Study conducted by EPA in 1974 (Keith et al. 1976). The reported concentrations were 1.6, 1.8, and 2.3 µg/L (ppb). The 1982 Ground Water Supply Survey conducted by EPA reported ethylbenzene in only 3 out of 466 random samples at a mean concentration of 0.8 µg/L (ppb) and a maximum concentration of 1.1 µg/L (ppb) (Cotruvo 1985). Chemical monitoring of 617 private and 1,174 public groundwater wells in the state of Wisconsin revealed that ethylbenzene was detected in 3 community and 12 private wells. The concentration of ethylbenzene detected exceeded the state's recommended drinking water advisory limit of 1,400 µg/L (ppb) in 9 of the 12 private wells, but no exceedences were observed in the public wells (Krill and Sonzongni 1986).

Ethylbenzene was infrequently detected in a comprehensive survey conducted by the United States Geological Survey (USGS) of volatile organic compounds in private and public groundwater wells used for drinking water (USGS 2006). Ethylbenzene was identified in 18 out of 3,497 aquifer samples at a median concentration of 0.035 µg/L for the 18 samples having positive detections. In an analysis of domestic groundwater wells, the median concentration of ethylbenzene was reported as 0.041 µg/L for samples having positive detections. Ethylbenzene was identified in 7 out of 1,083 samples obtained from public wells across the United States at a median concentration of 0.32 µg/L for samples having positive detections.

Although ethylbenzene does not appear to be a frequent contaminant in public water supplies, private residential wells near landfills, hazardous waste sites, or gas stations are more likely to contain detectable levels of this compound. Ethylbenzene was listed as one of the 58 most frequently detected chemicals associated with groundwater contamination near superfund sites (Knox and Canter 1994). Ethylbenzene was listed as having a medium priority with respect to its frequency of occurrence. Ethylbenzene has been detected in wells downgradient from landfills in Southern Ontario at concentrations ranging from 12 to 74 µg/L (ppb) (Barker 1987). Ethylbenzene was detected at levels of 1–22, 1–5, and <1 µg/L in groundwater 0–37, 50–114, and 170–254 meters, respectively, downgradient from a municipal landfill located in Grindsted, Denmark (Baun et al. 2000). Ethylbenzene was detected in groundwater from a representative monitoring well on a former gas-compressor site near South Lovedale, Oklahoma at a concentration of 220 µg/L (Jin et al. 2007).

Borden and Yanoschak (1990) compared ground and surface water quality impacts associated with North Carolina sanitary landfills. These authors found that ethylbenzene was detected at ≈25% of the waste

water effluents (receiving secondary treatment) and only 3% of the groundwater sampled in the vicinity of sanitary landfill sites. Groundwater monitoring at 479 hazardous waste disposal sites indicated that ethylbenzene, like the other 9 VOCs monitored, was detected at more than 100 of the 479 sites tested (Plumb 1991). Ethylbenzene was also one of the VOCs detected in groundwater samples from hazardous waste sites in all 10 EPA regions. Rosenfeld and Plumb (1991) reported that ethylbenzene was detected in groundwater at 19% of wood-treatment industry sites based on its frequency of detection and average concentration. Groundwater near an underground coal gasification site in northeastern Wyoming contained concentrations of ethylbenzene ranging from 92 to 400 µg/L (ppb) (Stuermer et al. 1982). Groundwater samples near a fuel spill in the Great Ouse Basin in Great Britain contained ethylbenzene concentrations as high as 1,110 µg/L (ppb) (Tester and Harker 1981).

6.4.3 Sediment and Soil

The median ethylbenzene concentration (dry weight) detected in sediment in the United States in 1980–1982 was 5 µg/kg (ppb) according to EPA's STORET water quality database (Staples et al. 1985). The compound was detected in 11% of 350 sediment samples analyzed. More recent data from the STORET database indicated that ethylbenzene was identified, but not quantified, in 25 out of 68 sediment samples obtained from January 2005 to March 2007 (EPA 2007i).

Ethylbenzene concentrations were analyzed in contaminated soil samples obtained from the site of a former crude oil and natural gas production facility near Los Angeles, California. Concentrations ranged from the limit of detection (0.005 mg/kg) to 160 mg/kg. Subsurface samples were collected from trenches, boreholes, and excavations; the highest concentrations were found in samples obtained through a borehole (Soukup et al. 2007).

6.4.4 Other Environmental Media

Data from the FDA Total Diet Study Market Basket Surveys collected between September 1991 and October 2003 indicate that ethylbenzene was detected in 82 different food items at a maximum concentration of 0.129 ppm (FDA 2006b). In a previous Market Basket Survey, ethylbenzene was identified in 15 out of 234 table-ready food items at an average concentration of 0.0146 ppm and a range of 0.00637–0.0387 ppm (Heikes et al. 1995). Trace concentrations of ethylbenzene have been reported in split peas (0.013 mg/kg [ppm]), lentils (0.005 mg/kg [ppm]), and beans (mean concentration 0.005 mg/kg [ppm]; maximum concentration 0.011 mg/kg [ppm]) (Lovegren et al. 1979). Ethylbenzene was reported as one of 227 organic chemicals present in roasted filbert nuts (Kinlin et al. 1972). Gorna-Binkul et al.

(1996) reported concentrations of ethylbenzene in orange peel (0.0236 µg/g [ppm] dry weight) and in parsley leaves (0.2567 µg/g [ppm] dry weight). The author reported that the differences in concentrations of the VOCs were dependent on the plant species and the morphological part of the plant analyzed. In underground parts (i.e., roots and bulbs) not directly exposed to polluted ambient air during growth, no VOC concentrations were detected. Biedermann et al. (1995) reported concentrations of several VOCs in extra virgin olive oil collected in northwest Italy. These authors measured ethylbenzene levels in raw olives of 6 µg/kg (ppb), which increased with time as they were milled to 25 µg/kg (ppb). Levels in the finished olive oils ranged from 11 to 27 µg/kg (ppb) depending on the preparation method used. These authors reported that while some of the ethylbenzene was accumulated in the olives in the orchards, a larger proportion was accumulated as a result of exposure of the oil to air in the milling areas. Ethylbenzene concentrations in olive oil increased from 6 to 235 ppb after 2 days of exposure. The authors concluded that the production process increased the concentration of ethylbenzene in the oil as a result of uptake from the air that was likely to be contaminated with gasoline vapors associated with small vehicles used to move the olives from area to area within the olive oil mill.

Ethylbenzene was also found to migrate from thermoset polyester cooking containers (composed of cross-linking chains of styrene) into belly pork during cooking (Gramshaw and Vandenburg 1995). Migration ranged from <6 to 34 µg/kg for ethylbenzene. The authors also found that the migration measured during the second use of the cookware was generally higher than that during the first use. These authors also reported that ethylbenzene concentrations in food cooked in foil-covered dishes was higher than that in the same food cooked uncovered. This was especially true for ethylbenzene that was more volatile than the styrene tested. Ehret-Henry et al. (1994) also reported migration of ethylbenzene from polystyrene containers into dairy products. Concentrations of ethylbenzene were 2–4 µg/kg for yogurt and 4 µg/kg for chocolate dessert.

Sack et al. (1992) conducted a survey of VOCs in 1,159 household items, including automotive products, household cleaners and polishes, paint related products, fabric and leather treatments, cleaners for electronic equipment, oils, greases, and lubricants, adhesive-related products, and miscellaneous products. Ethylbenzene was detected in 157 of 658 (24%) of the products tested. The highest mean ethylbenzene concentrations and percentage of products in each category in which ethylbenzene was detected are as follows; 7.2% w/w (wet weight) in 7.5% of automotive products, 2.4% w/w in 47.8% of paint-related products, and 1.0% w/w in 11.8% of fabric and leather treatments.

Hodgson et al. (1996) determined the contribution of environmental tobacco smoke (ETS) to concentrations of VOCs in smoking environments. These authors reported that the average emission factor for ethylbenzene for six brands of cigarettes was 101 µg/cigarette (range 83–142 µg/cigarette). The average concentration of ethylbenzene in five smoking areas ranged from 1.3 to 8.7 µg/m^3 (0.3–2 ppbv). Martin et al. (1997) determined the ETS yield of selected analytes, including ethylbenzene, for the 50 top-selling U.S. cigarette brand styles in 1991 and for the University of Kentucky Research cigarette, K1R4F. The ETS was generated by smokers in an environmental test chamber. The ethylbenzene concentrations measured were 8.68 µg/m^3 for full flavor cigarettes, 8.24 µg/m^3 for full flavor low tar cigarettes, and 8.72 µg/m^3 for ultra-low-tar cigarettes. The mean ethylbenzene concentration for all cigarettes was 8.50 µg/m^3. The mean ethylbenzene yields by tar category weighted by market share were 81.18 µg/cigarette for full flavor cigarettes, 76.79 µg/cigarette for full flavor low tar cigarettes, and 81.66 µg/cigarette for ultra low tar cigarettes. The mean ethylbenzene yield for all cigarettes was 79.57 µg/cigarette.

Ethylbenzene was not detected (at a detection limit of 0.025 mg/kg [ppm] wet weight) in any of the 97 biota samples collected from all STORET stations in 1980–1983 (Staples et al. 1985). Ethylbenzene was detected at low concentrations (0.8 ng/g [0.8 ppb]) in oyster tissue, but not in clam tissue from Lake Pontchartrain at Passes, Louisiana (Ferrario et al. 1985). The highest average ethylbenzene concentration measured in tissue of bottomfish from Commencement Bay in Tacoma, Washington was reported as 0.01 mg /kg (ppm) (Nicola et al. 1987).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The highest exposure to ethylbenzene for the general public is most likely to occur via inhalation associated with the use of self-service gasoline pumps or while driving a gasoline-powered motor vehicle especially in high traffic areas or in tunnels (Lawryk et al. 1995; Smith et al. 2008). Backer et al. (1997) performed a study that measured exposures associated with the pumping two different blends of fuel under cold conditions in Fairbanks, Alaska. The subjects in the study had significantly higher levels of gasoline components in their blood after pumping gasoline than before. The changes in VOC levels in blood were similar whether the individuals pumped regular or oxygenated gasoline. Prior to pumping regular gasoline, the median concentration of ethylbenzene in blood was 0.10 ppb (n=26) with a range of 0.02–0.73 ppb; after pumping, the median concentration was 0.16 ppb with a range of 0.06–1.40 ppb. Before pumping an oxygenated fuel blend that was 10% ethanol, the median concentration of

ethylbenzene in blood was 0.11 ppb (n=22) with a range of 0.04–0.55 ppb; after pumping, the ethanol blend, the median concentration was 0.16 ppb with a range of 0.06–0.64 ppb.

Janasik et al (2008) studied ethylbenzene exposure in six male volunteers who were subjected to an exposure chamber containing ethylbenzene as well as toluene, xylene, and mesitylene at concentrations emulating Polish occupational exposure standards of 100 mg/m^3. Blood and urine samples obtained from the volunteers were analyzed. Ethylbenzene concentrations in the blood ranged from 20 to 200 µg/L, while urine concentrations ranged from 1 to 152 µg/L (Janasik et al. 2008).

Lawryk and Weisel (1996) measured in-vehicle concentrations of selected gasoline-derived volatile organic compounds on 113 commutes through suburban New Jersey and 33 New Jersey/New York commutes. In a typical suburban commute, the mean in-vehicle concentration of ethylbenzene was 11.5±18.8 µg/m^3 (2.64±4.32 ppbv; n=52) under low ventilation conditions and 8.5±11.2 µg/m^3 (1.9±2.57 ppbv; n=43) under high ventilation conditions. On the New Jersey turnpike and in the Lincoln Tunnel, the mean in-vehicle concentrations of ethylbenzene were 8.8±10.8 µg/m^3 (2.0±2.48 ppbv; n=32) and 14.3±10.2 µg/m^3 (3.29±2.34 ppbv; n=32), respectively.

Ethylbenzene is ubiquitous in urban and rural atmosphere resulting from vehicular and industrial emissions (EPA 1988c). Tobacco smoke also provides a general source of exposure to ethylbenzene in indoor air (Wallace et al. 1987c). Wallace et al. (1989) also reported that two activities, painting and the use of automotive products (carburetor cleaner), led to increased indoor exposure to ethylbenzene by 100-fold. Indoor exposure to ethylbenzene may also be increased resulting from the start-up of gasoline-powered engines in attached garages (Dodson et al. 2008). Information on exposure from foods is limited, but is not likely to be a significant source of ethylbenzene for the general population.

Human exposure to styrene and ethylbenzene was assessed by considering inhalation exposure (including cigarette smoking) and food intake (Tang et al. 2000). The daily exposure to ethylbenzene for the general population was calculated as 1.8 µg/kg bodyweight/day, with up to 99% of the exposure due to inhalation routes and only 1–2% caused by food consumption.

One-half of the household drinking water used in the United States is supplied by groundwater, and contamination of groundwater by petroleum products is an increasingly common problem (Beavers et al. 1996). Beavers et al. (1996) conducted a study in a New England household that used groundwater contaminated by gasoline from a leaking underground storage tank. A total daily dose of 379 µg

ethylbenzene (204 µg ingested and 175 µg inhaled) was estimated for an exposed subject compared to a median daily dose of 32 µg for unexposed subjects. Of the 175 µg inhaled by the exposed subject, 108 µg was attributed to shower activities. The exposed subject and the three non-exposed subjects all were smokers.

The 1982 National Human Adipose Tissue Survey conducted by EPA measured ethylbenzene in 96% of the 46 composite samples analyzed for VOCs (EPA 1986). A wet tissue concentration range of not detected (detection limit=2 ng/g) to 280 ng/g (ppb) was reported, but an average concentration was not provided.

Ethylbenzene has been detected in breast milk samples collected from 8 of 12 women from various cities in the United States; however, the concentrations were not reported (Pellizzari et al. 1982). The 12 women sampled in the study were residents of Bayonne, New Jersey (6 women), Jersey City, New Jersey (2 women), Bridgeville, Pennsylvania (2 women), and Baton Rouge, Louisiana (2 women).

Mean and median concentrations of ethylbenzene detected in 631 blood samples from participants in the Third National Health and Nutrition Examination Survey (NHANES III 1998–1994 data) were 0.11 and 0.06 ppb (95 percentile value of 0.25 ppb), respectively (Ashley et al. 1994). In an earlier study (Ashley et al. 1992), these authors reported a mean ethylbenzene concentration of 0.12 ppb in 13 blood samples. Hajimiragha et al. (1989) conducted a study of 13 nonsmokers and 14 smokers with no known occupational or hobby-related exposure to volatile organic hydrocarbons. These authors reported a mean and median ethylbenzene concentration of 651 ng/L (0.651 ppb) and 431 ng/L (0.431 ppb) for the nonsmokers and 837 ng/L (0.837 ppb) and 533 ng/L (0.533 ppb) for the smokers. Ethylbenzene concentrations tended to occur at higher concentrations in the blood of smokers than in nonsmokers; however, the difference was not significant. Ashley et al. (1995) also reported that smoking elevated the blood levels of ethylbenzene and was highly correlated with blood levels of 2,5-dimethylfuran. These authors reported a mean concentration of 0.10 ng/mL (ppb) (median 0.048 ng/mL; range from below detection limit to 2.7 ng/mL) for nonsmokers and a mean concentration of 0.17 ng/mL (ppb) (median 0.16 ng/mL; range 0.036–0.88 ng/mL) for smokers. To aid in understanding the kinetics of uptake and elimination of volatile organics (including ethylbenzene), Ashley and Prah (1997) measured blood concentrations before, during, and after exposure of five individuals to a mixture of volatile organics in a controlled chamber. The half-lives of the compounds measured were <0.5 hour, but the elimination time courses were multiexponential and suggested that, with repeated exposure, bioaccumulation may occur in humans.

Occupational exposure to ethylbenzene in the petroleum industry has been reported in a study that measured ethylbenzene concentrations in air for 49–56 workers during the summer of 1984 (Rappaport et al. 1987). The average air concentrations of ethylbenzene measured over the full work shift for gasoline service station attendants, transport drivers, and outdoor refinery personnel were comparable at 0.063, 0.079, and 0.079 mg/m^3, respectively (14.5, 18.2, and 18.2 ppbv, respectively). The authors noted that exposures of service station attendants were significantly lower when vapor recovery systems were present. Crude oil process operators at an offshore processing plant near Norway were found to be exposed to 0.01–0.09 ppm of ethylbenzene in air during a full 12-hour work shift. Short-term exposure to ethylbenzene was dependent upon the specific work task and ranged from <0.01 to 1.11 ppm. Workers on the flotation package were found to be exposed to the highest ethylbenzene concentrations (Bratveit et al. 2007).

Personal air monitoring of 35 varnish workers (spraymen) has revealed an average ethylbenzene concentrations of 4.0 ppm, while the average concentration in blood was 61.4 µg/L (Angerer and Wulf 1985). Concentrations of ethylbenzene were monitored in auto paint shops in Spain that used organic solvents (de Medinilla and Espigares 1988). These authors reported air concentrations of ethylbenzene ranging from 0.50 to 125.0 mg/m^3 (0.12–28.75 ppmv).

The indoor air of screen printing plant workrooms located directly below houses in Amsterdam, Holland was found to contain median TWA concentrations of ethylbenzene ranging from <0.03 mg/m^3 (7 ppbv) to 1.30 mg/m^3 (299 ppbv) and maximum TWA concentrations ranging from 0.11 mg/m^3 (25 ppbv) to 3.21 mg/m^3 (738 ppbv) (Verhoeff et al. 1988).

Spray-painting and gluing operations can also result in exposure to ethylbenzene; personal air monitoring of workers measured average exposures of approximately 0.50 ppmv (2.2 mg/m^3) (Whitehead et al. 1984). Most of the operations measured during the study were performed in ventilation hoods.

Holz et al. (1995) reported that ethylbenzene air concentrations detected from air sampling in all areas of a styrene production facility located in the former German Democratic Republic ranged from 365 to 2,340 µg/m^3 (0.08–0.53 ppmv).

According to the National Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983, an estimated 201,838 workers were potentially exposed to ethylbenzene in the workplace (NIOSH

1990). The NOES database does not contain information on the frequency, concentration, or duration of occupational exposure to any of the chemicals listed. The survey provides only estimates of the numbers of workers for whom potential exposure in the workplace is an issue.

The Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) based on a TWA of 100 ppm (≈435 mg/m^3 at 1 atm and 25 °C) in the workplace (OSHA 1974). The American Conference of Governmental Industrial Hygienists also recommends a Threshold Limit Value (TLV-TWA) of 100 ppm (≈435 mg/m^3) for occupational exposures (ACGIH 1992). The recommended exposure limit (REL) for occupational exposures (TWA) set by the NIOSH is also 100 ppm (≈435 mg/m^3) for ethylbenzene based on a 10-hour average workday and a 40-hour workweek (NIOSH 2005).

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 ethylbenzene by inhalation in urban and rural atmospheres contaminated by vehicular and industrial emissions. Tobacco smoke also provides a general source for exposure of children to ethylbenzene in indoor air, especially in the homes where one or both parents smoke. Children may also be exposed to ethylbenzene-containing consumer products, such as carpet glues, paints, and varnishes. Household activities, such as painting, can lead to short-term exposures to higher levels of ethylbenzene if ventilation is inadequate. The limited information available on exposure from foods indicates that food is not likely to be a significant source of ethylbenzene for children.

Ethylbenzene is heavier than air, and since young children are closer to the ground or floor because of their height, during accidental exposures they may be exposed to more ethylbenzene vapors than adults. A 2- year monitoring study (2000–2001) involving 134 children aged 6–10 was conducted in Minneapolis, Minnesota in order to assess exposure to VOCs, including ethylbenzene (Sexton et al. 2005). The distribution of ethylbenzene measured in the blood of these children (416 samples) is provided in Table 6-3. Comparing these data to monitoring results from NHANES III, the levels of ethylbenzene in children's blood is approximately 2 or more times lower than in non-occupationally exposed adults (Sexton et al. 2005). Ethylbenzene has been detected in breast milk samples collected from 8 of 12 women from various cities in the United States; however, the concentrations were not reported (Pellizzari et al. 1982). The 12 women sampled in the study were residents of Bayonne, New Jersey (6 women); Jersey City, New Jersey (2 women); Bridgeville, Pennsylvania (2 women); and Baton Rouge, Louisiana (2 women). No direct pharmacokinetic experiments have been done to investigate whether significant amounts of ethylbenzene are transferred to breast milk in mammals. No studies were located that expressed the level of ethylbenzene or its metabolites in amniotic fluid, meconium, cord blood or neonatal blood.

Although no data were found in the literature, it is possible that children playing near hazardous waste sites could be dermally exposed to ethylbenzene in soil or orally exposed by hand-to-mouth activity and/or soil pica. Ethylbenzene, however, is only moderately adsorbed by soil. Since it has a moderately high vapor pressure, it will evaporate fairly rapidly from dry soil. However, under certain soil conditions, ethylbenzene may persist for longer periods of time; it has been detected in soil samples collected at 469 of the 829 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 2007). It was also detected in high concentrations in soil at a former crude oil and natural gas production facility, which was being considered for redevelopment (Soukup et al. 2007). No information was found concerning dermal and oral bioavailability of ethylbenzene in soil.

In the home, intentionally sniffing solvents could lead to high levels of exposure. Household products containing ethylbenzene, such as gasoline, paints, and glue, are widely available to children. Radhouame et al. (2008) studied inhalant abuse among 40 male and 4 female children and young adults (aged 11–23 years) suspected of drug abuse in Tunisia. Solvent metabolites were measured in urine samples to indicate exposure to VOC compounds through sniffing of various products. The authors concluded that the particular children in the study abused substances that ultimately resulted in high toluene and hexane exposures, as opposed to those resulting in high ethylbenzene exposure (Chakroun et al. 2008). However, abuse of household products could still be a concern for exposure of children to ethylbenzene.

Table 6-3. Distribution of Blood Ethylbenzene Concentrations in Children (ng/mL)

Sampling period	Samples	Percentage above detection limit	10th	25th	50th	75th	90th	95th	99th
February 2000	92	79.1	0.02	0.02	0.03	0.05	0.07	0.08	0.12
May 2000	86	66.7	0.01	0.02	0.03	0.04	0.05	0.07	0.17
February 2001	63	61.1	0.02	0.02	0.02	0.03	0.03	0.03	0.04
May 2001	88	98.9	0.03	0.04	0.05	0.06	0.08	0.09	0.10

Source: Sexton et al. 2005

No information was found concerning differences in the weight-adjusted intakes of ethylbenzene by children.

No exposures of children to ethylbenzene by contamination of workers' homes were found in the Workers' Home Contamination Study conducted under the Worker's Family Protection Act (NIOSH 1995).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to ethylbenzene (see Section 6.5), there are several groups within the general population that may receive potentially high exposures (higher than background levels) to ethylbenzene. These populations include individuals living in proximity to sites where ethylbenzene is produced or used in manufacturing or sites where ethylbenzene is disposed, and includes individuals living near the 829 NPL hazardous waste sites where ethylbenzene has been detected in some environmental media (HazDat 2007). Ethylbenzene has been detected in air and groundwater at 121 and 557 NPL hazardous waste sites, respectively.

Individuals living or working near petroleum refineries or chemical manufacturing plants may receive higher inhalation exposures than those experienced by the general population. Residents living in the vicinity of gasoline stations, high traffic areas, tunnels, parking lots, and highways may also receive a higher than average inhalation exposure since ethylbenzene is a component of gasoline (Smith et al. 2008). Residential wells downgradient of leaking underground storage tanks, landfills, and hazardous waste sites contaminated with petroleum products and solvents may contain high levels of ethylbenzene. If these residential wells are the primary source of drinking water, this may pose a risk to human health via consumption of contaminated water as well as increased inhalation of and dermal contact with ethylbenzene during showering and bathing. A study of indoor air in a home using gasoline-contaminated drinking water found that exposures to ethylbenzene could occur via inhalation during showering and other household activities (Beavers et al. 1996). Ethylbenzene concentrations in shower air were often one to two orders of magnitude higher than non-shower air. These authors reported a total daily household dose of ethylbenzene of 379 μg, with 204 μg derived from ingestion of drinking water and 175 μg derived from inhalation (108 μg from shower-related inhalation and 67 μg from non-shower-related inhalation) to the exposed subject living in the home. The daily dose of ethylbenzene for an unexposed smoker by comparison was estimated to be 32 μg.

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 ethylbenzene 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 ethylbenzene.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of ethylbenzene are well characterized (see Table 4-2) and allow prediction of the transport and transformation of the compound in the environment (Amoore and Hautala 1983; Bohon and Claussen 1951; Chiou et al. 1983; EPA 1982; Hansch and Leo 1979; Hodson and Williams 1988; Mackay and Shiu 1981; Polak and Lu 1973; Sutton and Calder 1975; Verschueren 1983). No additional studies are needed at the present time.

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 2006, became available in May of 2008. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Ethylbenzene has numerous uses (ACGIH 2002; Ransley 1984; Verschueren 1983), and production of the chemical has steadily increased since 1983 (C&EN 1994a, 1994b, 1995, 2006; Kirschner 1995). Releases occur from a variety of common sources including manufacturing and production (TRI06 2008), fuels, automobile exhaust, and fumes from paints, varnishes, solvents, carpet glue, and hot asphalt (Fishbein 1985; Hampton et al. 1983; Junk and Ford 1980; Katzman and Libby 1975; Kitto et al. 1997; Mukund et al. 1996; NAS 1980; Wallace et al. 1987b). Ethylbenzene also is released from waste waters to the

atmosphere in municipal sewer systems (Quigley and Corsi 1995). Therefore, the potential for human exposure to ethylbenzene is considerable. The medium most likely to be contaminated is air, although ethylbenzene has also been detected in trace amounts in water supplies. Some ethylbenzene-containing wastes are designated as hazardous and are subject to EPA handling and recordkeeping requirements. Recommended methods for the disposal of ethylbenzene include burial in a landfill and rotary kiln incineration, liquid injection incineration, and fluidized bed incineration (EPA 1981d). No data need is identified at this time.

Environmental Fate. Ethylbenzene is primarily partitioned to and transported in air (Dewulf and van Langenhove 1997; Eisenreich et al. 1981; Mackay 1979; Masten et al. 1994). The partitioning and transport processes in water, soil, and aquatic life are also well characterized (ASTER 1995; Dewulf et al. 1996; Kawamura and Kaplan 1983; Ligocki et al. 1985; Swann et al. 1983). Transformation and degradation processes have also been well characterized in air (Atkinson and Carter 1984; Atkinson et al. 1978; Grovenstein and Mosher 1970; Herron and Huie 1973; Hoshino et al. 1978; O'Brien et al. 1975; Ohta and Ohyama 1985; Ravishankara et al. 1978; Yanagihara et al. 1977), water (Acton and Barker 1992; Anid et al. 1993; Bouwer and McCarty 1984; Burback and Perry 1993; Ehrhardt and Petrick 1984; Gschwend et al. 1982; Hutchins 1991; Masten et al. 1994; Wakeham et al. 1983; Wilson et al. 1986), and in soil and sediment (Bestetti and Galli 1984; Chen and Taylor 1995; Hutchins 1991; Hutchins et al. 1991; Jamison et al. 1970; Ramanand et al. 1995; Van der Linden and Thijsse 1965; Yadav and Reddy 1993; Zappi et al. 1996). No data need is identified at this time.

Bioavailability from Environmental Media. Ethylbenzene is absorbed following inhalation, oral, and dermal exposures. Information is available on its absorption from air and water, but little data exist regarding dermal bioavailability and absorption from soil and food. Due to its large vapor pressure and Henry's law constant, ethylbenzene is expected to volatilize fairly rapidly from soil surfaces. Based on the moderate affinity of ethylbenzene for soil, especially soils with relatively high organic carbon content, the amount of ethylbenzene in bioavailable form in soil is expected to be low to moderate. Because of the low BCF values calculated for ethylbenzene, food chain bioaccumulation would not be expected to be significant sources of ethylbenzene exposure. No data need is identified at this time.

Food Chain Bioaccumulation. Limited data suggests that ethylbenzene does not bioconcentrate in aquatic organisms (Ogata et al. 1984), and is not likely to bioaccumulate in aquatic or terrestrial food chains. However, little information on food residues in commercially important fish and shellfish species

is currently available. Additional monitoring data regarding the levels of ethylbenzene would be helpful for several commercially important fish and shellfish species.

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

An extensive amount of atmospheric monitoring data exists (EPA 1988c; Goldberg et al. 1995; Kinney et al. 2002; Kostiainen 1995; Mukerjee et al. 1997; Quigley and Corsi 1995; Wallace et al. 1987a, 1987c; Zielinska et al. 1996; Zweidinger et al. 1988). Ethylbenzene has also been detected in surface water and groundwater (Barker 1987; Borden and Yanoschak 1990; Chen and Zoltek 1995; Cole et al. 1984; Cotruvo 1985; Gschwend et al. 1982; Krill and Sonzongni 1986; Quigley and Corsi 1995; Staples et al. 1985; Stubin et al. 1996; Stuermer et al. 1982; Tester and Harker 1981), sediment (Staples et al. 1985), a limited number of foodstuffs (Ferrario et al. 1985; Górna-Binkul et al. 1996; Kinlin et al. 1972; Lovegren et al. 1979; Nicola et al. 1987), and in cigarette smoke (Hodgson et al. 1996; Martin et al. 1997; Wallace 1986; Wallace et al. 1987c). Continued monitoring data at or around hazardous waste sites are needed in order to assess human exposure for populations residing in these areas.

Exposure Levels in Humans. Ethylbenzene and its metabolites have been detected in human blood (Angerer and Wulf 1985; Ashley et al. 1994), urine (Bardodej and Bardodevova 1970; Dutkiewicz and Tyras 1967; Engstrom and Bjurstrom 1978; Gromiec and Piotrowski 1984; Kiese and Lenk 1974; Sullivan et al. 1976; Yamasaki 1984), breast milk (Pellizzari et al. 1982), and adipose tissue (Engstrom and Bjurstrom 1978; EPA 1986). Most of the monitoring data have come from occupational studies of specific worker populations exposed by inhalation. Members of the general population can be exposed to ethylbenzene through inhalation of fumes while pumping gas, riding in gasoline-powered vehicles, and routinely starting vehicles in enclosed garages (Backer et al. 1997; Dodson et al. 2008; Lawryk and Weisel 1996; Lawryk et al. 1995), as well as exposure to ethylbenzene-containing consumer products (Hodgson et al. 1991; Lillo et al. 1990; NAS 1980; Otson et al. 1994; Sack et al. 1992; Wallace et al. 1987b). Additional information regarding the general population's exposure to ethylbenzene would be useful. Dietary intake is expected to be insignificant as compared to inhalation exposure (Tang et al. 2000). Oral exposures are likely to be low, except for the consumption of contaminated drinking water by populations living in the vicinity of hazardous waste sites, leaking underground storage tanks, or

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

Exposures of Children. Children are exposed to ethylbenzene by the same routes that affect adults. Biomonitoring data suggest that blood levels of ethylbenzene are lower in children than non--occupationally exposed adults (Sexton et al. 2005). Ethylbenzene has been detected in breast milk samples collected from 8 or 12 women from various cities in the United States; however, the concentrations were not reported (Pellizzari et al. 1982). There do not appear to be any childhood specific means to decrease exposure to ethylbenzene, aside from educating children about the dangers of inhalant abuse (Chakroun et al. 2008). A data need exists to determine current ethylbenzene residues and their sources in breast milk of members of the general population.

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 ethylbenzene 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

The Federal Research in Progress (FEDRIP 2007) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-4.

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 ethylbenzene 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.

Table 6-4. Ongoing Research Regarding the Environmental Fate and Exposure to Ethylbenzene

Investigator	Affiliation	Description	Sponsor
Thrall KD	Battelle Pacific Northwest Laboratories, Richland, Washington	The overall research objective for this project is to expand prior studies to evaluate the percutaneous absorption of compounds commonly encountered within similar industries (styrene and ethylbenzene) along with focused studies to evaluate the dermal bioavailability of compounds with both lipophilic and hydrophilic properties.	NIOSH
Burke J	EPA	The development of a human exposure model has been initiated to characterize population exposures to air toxics in support of risk assessment activities in the National Air Toxics Program. This research will develop probabilistic inputs for exposure to chemicals such as benzene and ethylbenzene for use in the model.	EPA

EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health

Source: FEDRIP 2007

7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Ethylbenzene can be determined in biological fluids, and tissues, and breath using a variety of analytical methods. Representative methods are summarized in Table 7-1. Most analytical methods for biological fluids and tissues use headspace gas chromatographic (GC) analysis. Breath samples are usually collected on adsorbent traps or in sampling bags or canisters, and then analyzed by GC.

The headspace method involves equilibrium of volatile analytes such as ethylbenzene between a liquid or solid sample phase and the gaseous phase. The gaseous phase is then analyzed by GC. There are two main types of headspace methodology: static (equilibrium) headspace and dynamic headspace, which is usually called the "purge-and-trap" method (Seto 1994). The static headspace technique is relatively simple, but may be less sensitive than the purge-and-trap method. The purge-and-trap method, while providing increased sensitivity, requires more complex instrumentation and may result in artifact formation (Seto 1994). Generally, an inert gas such as helium is passed over the biological sample at elevated temperature, and the purged volatile organic compound (VOC) is trapped onto an adsorbent polymeric resin (Tenax). The organic compound is thermally desorbed from the adsorbent followed by identification and quantitation using various detectors; flame ionization detection (FID) and mass spectrometry (MS) are used most often. Other sample preparation methods have been used, but less frequently. Solvent extraction permits concentration, thereby increasing sensitivity, but the extraction solvent can interfere with analysis. Direct aqueous injection is a very rapid method, but sensitivity is low and matrix effects can be a serious problem.

Table 7-1. Analytical Methods for Determining Ethylbenzene in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Whole blood	Whole blood samples were collected by venipuncture, sealed, and refrigerated. Extraction accomplished using a closed system purge and trap sampler	Capillary GC/MS	0.015–0.020 ppb	114–118	Ashley et al. 1992, 1994
Blood	Direct analysis via inertial spray extraction interface	GC/MS	<1 ppb	No data	St-Germain et al. 1995
Blood	Automated head space	Capillary GC/FID	0.002 µg/mL	90–110 (estimated)	Otson and Kumarathasan 1995
Blood	Extraction using dynamic headspace purge and trap system followed by thermal desorption to the GC	cap GC/FID	50 ng/L (calculated)	39	Fustinoni et al. 1996
Blood	Capillary blood samples extracted, sealed, mixed, and refrigerated. Gas phase sampled with gastight syringe and injected on column	GC/FID	2.7 µg/L	No data	Janasik et al. 2008
Urine	Purge and trap	Capillary GC/MS	No data	64–123 for model compounds	Michael et al. 1980
Urine	Extraction using dynamic headspace purge and trap system followed by thermal desorption to the GC	Capillary GC/FID	50 ng/L (calculated)	61	Fustinoni et al. 1996
Urine	Extracted to headspace	GC/FID	0.48 µg/L	No data	Janasik et al. 2008
Mother's milk	Purge and trap	Capillary GC/MS	No data	35–88 for model compounds	Michael et al. 1980
Brain tissue (post mortem)	Modified headspace (full evaporation technique)	Capillary GC-ITD	0.038 nmoles/sample	80–120	Schuberth 1996
Fat tissue	Add saline; freeze; thaw to 0 °C prior to analysis; add CS_2; inject into GC	GC/FID; confirmation GC/MS	No data	No data	Wolff et al. 1977
Adipose tissue	Purge and trap	Capillary GC/MS	No data	13–80 for halogen-ated hydro-carbons	Michael et al. 1980
Breath	Collection via spirometer into passivated canisters	Capillary GC/MS	low $\mu g/m^3$ levels	77–82	Thomas et al. 1991

Table 7-1. Analytical Methods for Determining Ethylbenzene in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Breath	Collection via spirometer onto charcoal traps; microwave desorption	Capillary GC/MS-SIM	0.2 µg/m^3 (1 L sampled)	No data	Riedel et al. 1996

FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; ITD = ion trap detector; MS = mass spectrometry; SIM = selected ion monitoring

A spirometer is usually used for the collection of breath samples. The device is used to provide clean air for inhalation and a mechanism for pumping exhaled breath into the collection media (Pellizzari et al. 1985). The breath samples are collected into Tedlar bags with subsequent adsorption onto Tenax traps (Pellizzari et al. 1985) or into passivated stainless steel canisters (Thomas et al. 1991). The Tenax traps are analyzed by thermal desorption GC techniques, and canister samples are analyzed by GC as well.

A sensitive and reliable method for identification and quantitation of ethylbenzene in samples of whole blood taken from humans following exposure to VOCs has been developed by Ashley and coworkers at the Centers for Disease Control and Prevention (Ashley et al. 1992, 1994). The method involves purge-and-trap of a 10-mL blood sample with analysis by capillary GC/MS. Anti-foam procedures were used, as well as special efforts to remove background levels of VOCs from reagents and equipment (Ashley et al. 1992). The method is sensitive enough (ppt levels) to determine background levels of VOCs in the population and provides adequate accuracy (114–118% recovery) and precision (16–44% relative standard deviation [RSD]) for monitoring ethylbenzene in the population. Using GC/FID to analyze capillary blood samples, Janasik et al. (2008) achieved a detection limit of 2.7 µg/L for ethylbenzene.

Few methods are available for the determination of ethylbenzene in body fluids and tissues other than blood. A modified dynamic headspace method for determination of ethylbenzene in urine, mother's milk, and adipose tissue has been reported (Michael et al. 1980). Volatiles swept from the sample are analyzed by capillary GC/FID. Acceptable recovery was reported for model compounds, but detection limits were not reported (Michael et al. 1980). Ethylbenzene in brain tissue may be determined using a headspace, capillary/ion trap detector (ITD) technique (Schuberth 1996). Recovery was good (80–120%) as was precision (≈20% RSD); the detection limit was reported as 4 ng/sample (0.038 nmoles) (Schuberth 1996). Janasik et al. (2008) achieved a detection limit of 0.48 µg/L for detection of ethylbenzene in urine using GC/FID. Biological monitoring for exposure to VOCs can also be based on identification of metabolites in urine, as analyzed by GC (Janasik et al. (2008). Sensitive, reliable methods are available for measuring ethylbenzene in breath. Exhaled breath is collected using a spirometer. The exhaled breath is collected into Tedlar bags for later transfer to adsorption tubes (Wallace et al. 1982), into passivated canisters (Thomas et al. 1991), or directly onto adsorbent traps (Riedel et al. 1996). The spirometer system, using adsorption onto Tenax traps and analysis by thermal desorption/capillary GC/MS techniques, was field-tested over the course of a very large exposure study (EPA 1987). The quantitation limit was ≈1 µg/m^3, recovery was 91–100%, and the precision for duplicate samples was ≤30% RSD (EPA 1987). Advances in the methodology include development of a more compact system with collection in 1.8-L canisters

(Thomas et al. 1992). Recovery of ethylbenzene is 92–104%, precision for duplicate samples is <3% RSD, and the detection limit was estimated as 3 μg/m^3 for ethylbenzene (Thomas et al. 1992).

7.2 ENVIRONMENTAL SAMPLES

Methods are available for determining ethylbenzene in a variety of environmental matrices. A summary of representative methods is shown in Table 7-2. Validated methods, approved by agencies and organizations such as EPA, ASTM, APHA, and NIOSH, are available for air, water, and solid waste matrices. Gas chromatography is the most widely used analytical technique for quantifying concentrations of ethylbenzene in environmental matrices. Various detection devices used for GC include FID, MS, and the photoionization detector (PID). Because of the complexity of the sample matrix and the low concentration of VOCs in most environmental media, sample preconcentration is generally required prior to GC analysis. Air samples may be collected and concentrated on adsorbent or in canisters for subsequent analysis. Methods suitable for determining trace amounts of ethylbenzene in aqueous and other environmental media include three basic approaches to the pretreatment of the sample: gas purge-and-trap technique, headspace gas analysis, and extraction with organic solvent.

Gas purge-and-trap is the most widely used method for the isolation and concentration of VOCs in environmental samples (Lesage 1993). The purge-and-trap technique offers advantages over other techniques in that it allows facile isolation and concentration of target compounds, thereby improving overall limits of detection and recovery of sample. Detection limits of <1 μg of ethylbenzene per liter of sample have been achieved (APHA 1995c; EPA 1984c, 1991b, 1992a). A serious drawback of this technique, particularly for quantitative analysis, is interference by impurities found in the stripping gas (EPA 1994c).

A purge-and-trap method with GC/FID analysis (Otson and Williams 1982) or GC/MS (Otson and Chan 1987) has been reported for the analysis and quantitation of ethylbenzene in environmental samples. Detection limits of <0.1 μg/L for GC/FID analysis and 0.1 μg/L were reported. Accuracy was also good, 74–88% (Otson and Chan 1987; Otson and Williams 1982).

Extraction with organic solvents (liquid-liquid extraction) provides a simple, rapid screening method for semi-quantitative determination of ethylbenzene in aqueous samples containing limited number of VOCs, but is less effective for aqueous samples containing large numbers of VOCs. Furthermore, interference

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air	Collection on charcoal adsorbent tube; desorption with CS_2	GC/FID	0.001–0.01 mg/sample[a]	Bias -7.6%	NIOSH 1994a (NIOSH Method 1501)
Occupational air	Organic vapor passive dosimeter badges; desorbed using CS_2	GC/MS	0.01 ppm	No data	Bratveit et al. 2007
Ambient air	Collection on Tenax adsorbent; thermal desorption	Capillary GC/MS	20 ng estimated[a]	No data	EPA 1988a (Method TO-1)
Ambient air	Collection in passivated stainless steel canisters	Capillary GC/MS or PID or FID	No data	No data	EPA 1988b (Method TO-14)
Ambient air	Collection on Tenax adsorbent; thermal desorption	Capillary GC/MS	2 ng[a]	No data	Pellizzari et al. 1993 (IARC Method 6)
Ambient air	Collection in canisters	GC/MS	0.2 ppbv	bias -8.1%	McClenny and Fortune 1995 (CLP Method)
Ambient air	Collection on multisorbent traps; automated preconcentration	Capillary GC/MS	0.036 ppbv	102	Oliver et al. 1996
Ambient air	Collection on multisorbent traps; thermal desorption with modified cryofocussing	Capillary GC/FID	0.25 ppbv	98	Oliver et al. 1996
Indoor air	Collection on Tenax acsorbent; thermal desorption	GC/MS	0.05–0.2 µg/m^3	No data	Kostianinen 1995
In-vehicle air	Collection on Tenax or multisorbent traps; thermal desorption	Capillary GC/MS-SIM	No data	No data	Lawryk and Weisel 1996
Flue gas	Collection on adsorbent traps using probe; thermal desorption	Capillary GC/FID	0.05 µg/m^3 (estimated)	No data	Jay and Steiglitz 1995
Product emissions	Collection on charcoal traps; desorption with CS_2	Capillary GC/FID	No data	No data	Wadden et al. 1995
Tobacco smoke	Collection on multisorbent traps; thermal desorption	fused-silica PLOT column GC/MS	No data	No data	Barrefors and Petersson 1993

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Snow	SPME using DVB-coated PDMS fiber with a film thickness of 65 µm	GC/MS	0.20 µg/L	No data	Kos and Ariya 2006
Drinking water	Purge and trap	GC/PID	0.01–0.04 µg/L	98–101	EPA 1991a (EPA Method 502.2)
Drinking water	Purge and trap	GC/PID; confirmation on second column or GC/MS	0.002 µg/L	93	EPA 1991b (EPA Method 503.1)
Drinking water	Purge and trap	GC/MS	1–2 µg/L	No data	EPA 1991c (EPA Method 524.1)
Drinking water	Purge and trap	Capillary GC/MS	0.06 µg/L	96–99	EPA 1992a (EPA Method 524.2)
Drinking water	Purge and trap	GC/FID or GC/MS	low µg/L	84–114	ASTM 1999b (ASTM Method D 3871)
Drinking water	Direct injection	GC/FID	~1 mg/L	No data	ASTM 1999a (ASTM Method D 2908)
Waste water	Purge and trap	GC/PID; confirmation on second column	0.2 µg/L	98	EPA 1984c (EPA Method 602)
Waste water	Purge and trap	GC/MS	7.2 µg/L	100–103	EPA 1999 (EPA Method 624)
Water	Closed-loop stripping	Capillary GC/MS	50 ng/L (instrumental)	No data	APHA 1995a (Method 6040B)
Waste water	Purge and trap	GC/MS	7.2 µg/L		APHA 1995b (Method 6210B)
Waste water	Purge and trap	GC/PID; confirmation on second column or GC/MS	0.2 µg/L	93	APHA 1995c (Method 6220B)
Waste water	Purge and trap	GC/PID	0.01–0.05 µg/L	93	APHA 1995d (Method 6220C)

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Solid waste	Direct injection or purge and trap	Capillary GC/PID	~1 µg/L (soil, sediment); ~0.1 mg/kg (wastes)	101	EPA 1994d (SW846 Method 8021A)
Solid waste	Purge and trap	Capillary GC/PID	~1 µg/L (soil, sediment); ~0.1 mg/kg (wastes)	101	EPA 1995a 9SW846 Method 8021B, proposed)
Solid waste	Purge and trap	Capillary GC/MS	~5 µg/kg (soil, sediment)	99	EPA 1994e (SW846 Method 8260A)
Solid waste	Various options including purge and trap, headspace, closed system vacuum distillation	Capillary GC/MS	purge and trap: ~5 µg/kg (soil and sediment); ~0.5 mg/kg (wastes)	90–112 (purge and trap)	EPA 1995b (SW846 Method 8260B, proposed)
Plant foliage	Solvent extraction; filtration	Capillary GC/SM-SIM	50 pg/µL extract	No data	Keymeulen et al. 1991
Fish	Solvent extraction; cleanup on florisil column; solvent microextraction	GC/FID	5 µg/g[b]	98–102	Karasek et al. 1987
Fish and sediment	Homogenization; freezing and vacuum extraction	Capillary GC/MS	25 ppb[b]	Sediments, 97 recovery; fish, 76% average for all analytes	Hiatt 1981, 1983
Eggs	Headspace	Capillary GC/PID; confirmation by GC/MS	0.002 µg/mL	94 (white); 49 (whole); 21 (yolk)	Stein and Narang 1990
Fruits and vegetables	Solvent extraction; filtration	Capillary GC/MS-SIM	No data	No data	Górna-Binkul et al. 1996
Olives and olive oil	Headspace	Capillary GC/MS	Low µg/kg levels	No data	Biedermann et al. 1995

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cooked meat	Azeotropic distillation using Kilens-Nickerson estractor	Capillary GC/MS	6 µg/kg	No data	Gramshaw and Vandenburg 1995
Food containers (polystyrene)	Incubation with DMF; headspace	Capillary GC/FID; confirmation GC/MS	10 ppm	96–102	Sugita et al. 1995

[a]Sample detection limit will depend upon volume sampled. Value is estimated instrumental detection limit.
[b]Method detection limits were not provided; estimates cited are based on lowest concentrations used for method performance evaluation.

CS_2 = carbon disulfide; DMF = dimethylformamide; DVB = divinylbenzene; FID = flame ionization detector; GC = gas chromatography; MeOH = methanol; MS = mass spectrometry; PDMS = polydimethylsiloxane; PID = photoionization detector; PLOT = pourous-layer open tubular; SIM = selected ion monitoring; SPME = solid phase microextraction; UV = ultraviolet spectrophotometry

from the organic extraction solvent (hexane) makes it more difficult to completely identify all components (Karasek et al. 1987; Otson and Williams 1981).

Ethylbenzene may be determined in occupational air using collection on multisorbent cartridges, solvent desorption and analysis by GC/FID (NIOSH 1994a). Accuracy is very good (-7.6% bias); detection limits depend upon the amount of air sampled. Ambient air samples may also be collected on adsorbent traps (EPA 1988a; Pellizzari et al. 1993) or in stainless steel canisters (EPA 1988b; McClenny and Fortune 1995). Recovery for Tenax traps is very good, ranging from 91 to 100% (EPA 1987), and detection limits of 0.01 ppm have been reported (Bratveil et al. 2007). Little information on accuracy is available for multisorbent traps, but good recovery (102%) has been reported (Oliver et al. 1996). Bias of -8.1% for canister collection has been reported (McClenny and Fortune 1995). Detection limits depend upon the amount of air sampled, but values in the sub-ppb range have been reported (Kostiainen 1995; McClenny and Fortune 1995; Oliver et al. 1996). Organic vapor passive dosimeter badges may be used to determine personal exposure; the hydrocarbons are desorbed and analyzed by GC with GC/MS. Detection levels of 0.01 ppm for ethylbenzene have been reported (Bratveit et al. 2007). Purge-and-trap methodology is used most often for determination of ethylbenzene in water and hazardous wastes (Lesage 1993). The method was developed by Bellar and Lichtenberg (1974) for waste water. An inert gas is bubbled through the sample to strip out volatile components. The analytes in the gas stream are adsorbed onto sorbent traps, then thermally desorbed into the GC column. Very low detection limits for drinking water are reported for the purge-and-trap method with GC/PID (0.002–0.04 µg/L) (EPA 1991b). Accuracy is very good (93–101% recovery) (EPA 1991b). While the method is quite selective, confirmation using a second GC column or GC/MS is recommended (EPA 1991b). A sensitive (0.06 µg/L) and reliable method (96–99% recovery; <10% RSD) for drinking water uses capillary column GC/MS (EPA 1992a). Purge-and-trap methodology with analysis by GC/PID or GC/MS is used for waste waters (APHA 1995b, 1995c, 1995d; EPA 1984c, 1999). The detection limits are lower for GC/PID (0.2 µg/L) (EPA 1984c) than for GC/MS (7.2 µg/L) (EPA 1984b), but confirmation on a second column is recommended (EPA 1984c) when PID is used. Recovery and precision are very good (98–103% recovery; ≤10% RSD) (EPA 1984c, 1999).

Soil, sediment, and solid waste samples are difficult to analyze. Volatilization during sample handling and homogenization can result in ethylbenzene losses. The wet sample is usually dispersed in a solvent, then added to water for purge-and-trap/GC analysis (EPA 1994c; Minnich et al. 1997) or analyzed by high performance liquid chromatography (HPLC) (Dawson et al. 2008). Capillary GC/PID or GC/MS analysis provides detection limits in the low ppb range for soil and sediment and in the sub-ppm range for

solid wastes (EPA 1994d, 1994e, 1995a, 1995b). Minnich et al. (1997) reported detection limits as low as 1.7 ng/g using the GC method.

Few methods are available for the determination of ethylbenzene in fish and biota. A method for the determination of ethylbenzene in fish at low ppm levels using solvent extraction with GC/FID analysis has been reported (Karasek et al. 1987). A procedure to identify and quantify ethylbenzene in fish samples by vacuum distillation with capillary column GC/MS has been reported (Hiatt 1981, 1983). Recovery of 98–102% from spiked fish tissue was reported, but detection limits were not reported (Hiatt 1981). Purge-and-trap/capillary GC/MS has also been used for the determination of ethylbenzene in fish. Performance data for fish tissue samples were not reported (Dreisch and Munson 1983).

Few methods are available for the determination of ethylbenzene in food. Available methods involve solvent extraction (Górna-Binkul et al. 1996), headspace purge (Biedermann et al. 1995), and azeotropic distillation (Gramshaw and Vandenburg 1995) followed by capillary GC/MS or GC/PID analysis. Detection limits are in the low µg/kg range (Biedermann et al. 1995; Gramshaw and Vandenburg 1995). Little performance data are available. Recoveries from 21% (egg yolk) to 94% (egg white) were reported for headspace/capillary GC/PID analysis of eggs (Stein and Narang 1990).

Screening methods and field-portable methods may be useful analytical tools. Soil screening for petroleum hydrocarbons, including ethylbenzene, can be conducted using immunoassay procedures (EPA 1995e). Sensitivity is in the ppm range. Solid phase microextraction (SPME) has been tested as a screening method for water (Shirey 1995). The method is used in conjunction with capillary GC techniques. Portable GCs have been used for field monitoring of air (Berkley et al. 1991), water (Driscoll and Atwood 1993), soil (Driscoll and Atwood 1993), and hazardous waste (Overton et al. 1995). There are several studies that compare portable GC methods with laboratory methods (Berkley et al. 1991; Driscoll and Atwood 1993).

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 ethylbenzene 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 ethylbenzene.

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Exposure to ethylbenzene can be determined by the detection of mandelic acid and phenylglycolic acid in urine or by direct detection of ethylbenzene in human blood. Environmental exposures to ethylbenzene can result in detectable levels in human tissues. Existing methods for the determination of ethylbenzene in blood have the sensitivity necessary (0.008–0.012 ppb) (Ashley et al. 1992) to detect and measure low to trace levels of ethylbenzene in blood that might be present in the general population, as well as concentrations of ethylbenzene that might be associated with specific health effects. Methods for measurement of ethylbenzene in exhaled breath are sensitive enough (low $\mu g/m^3$) (Thomas et al. 1991) to provide background levels of ethylbenzene in the general population as well as to measure exposure. Additional performance information would be helpful, as would further development of a portable breath collection system. Information on levels of ethylbenzene in tissues is limited and the existing methods are not as well characterized. Improvements in the sensitivity of the methods for measuring concentrations of ethylbenzene in tissues and additional performance data would be helpful.

Methods for measuring metabolites and biomarkers for ethylbenzene are shown in Table 7-3. Methods exist for measuring ppm levels of ethylbenzene metabolites in urine (Ogata and Taguchi 1987, 1988; Sollenberg et al. 1985). They are sufficiently sensitive for measuring occupational exposure to ethylbenzene. These analytical methods are reliable and precise, but may not be sensitive enough to measure non-occupational exposure. Improvements in the sensitivity of the methods for measuring concentrations of ethylbenzene in tissues, and improvements in the sensitivity for measurement of metabolites in urine would allow better assessment of the correlation between levels in these media and observed health effects.

Table 7-3. Analytical Methods for Determining Biomarkers of Ethylbenzene in Biological Materials

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy percent recovery	Reference
Urine (MA)	Dilution; centrifugation	HPLC/UV	MA 5 ng injected	MA 100–102	Ogata and Taguchi 1988
Urine (MA and PGA)	MeOH addition; centrifugation	HPLC	PGA $8.5x10^3$ µg/L MA $10x10^3$ µg/L	PGA 101 MA 102.6	Ogata and Taguchi 1987
Urine (MA and PGA)	Filtration; solvent extraction; evaporation and dissolution	HPLC/UV	MA, PGA $1.5x10^3$ µg/L	No data	Sollenberg et al. 1985
Urine (MA and PGA)	Filtration; solvent extraction; evaporation and dissolution	ITP	MA $6.1x10^3$ µg/L PGA $3.0x10^3$ µg/L	No data	Sollenberg et al. 1985

HPLC = high performance liquid chromatography; ITP = isotachophoresis; MA = mandelic acid; PGA = phenylglyoxylic acid; UV = ultraviolet (detection)

Effect. No specific biomarkers of effect for ethylbenzene were identified.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Sensitive methods are available for measuring background levels of ethylbenzene in air, water, and wastes, the media of most concern for exposure of the general population and those populations located near hazardous waste sites. Few methods are available for measuring levels of ethylbenzene in fish, plants and biota. Detection limits in the low ppb range have been reported (Dreisch and Munson 1983; Hiatt 1981; Karasek et al. 1987; Keymeulen et al. 1991), but other performance data are generally lacking. Few methods are available for measuring levels of ethylbenzene in food. Little performance data are available for the available methods. Although several good analytical methods are available for detecting ethylbenzene in some environmental media, validated, reliable methods for measuring ethylbenzene in fish and foods are needed. These would be helpful in evaluating the potential for human exposure and health effects that might result from ethylbenzene contamination.

Methods for detecting environmental degradation products of ethylbenzene in environmental media are summarized in Table 7-4. Although methods are available for detecting major environmental degradation products (1-phenylethanol, acetophenone, benzaldehyde, for example) in reaction mixtures, it is not known whether these methods have the sensitivity and specificity for application to environmental media. Sensitive, reliable methods for determining degradation products in air, water, and waste would be helpful.

7.3.2 Ongoing Studies

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 ethylbenzene 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 ppt range.

Table 7-4. Analytical Methods for Determining Environmental Degradation Products of Ethylbenzene

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy percent recovery	Reference
Reaction mixtures	Solvent extraction; concentration	Capillary GC/FID	No data	No data	Ehrhardt and Petrick 1984
Reaction mixtures	Centrifugation; solvent extraction; concentration	GC/FID; confirmation GC/MS	No data	No data	Fukuda et al. 1989

FID = flame ionization detector; GC = gas chromatography; MS = mass spectrometry

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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 ethylbenzene based on a BMCL for auditory threshold shifts observed in rats exposed to ethylbenzene 8 hours/day for 5 days (Cappaert et al. 2000). The BMCL was estimated using an internal dose metric to simulate time averaged arterial blood concentration of ethylbenzene; a human equivalent concentration (HEC) of the BMCL was estimated using a human PBPK model. This $BMCL_{HEC}$ of 154.26 ppm was divided by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability).

ATSDR has derived an intermediate-duration inhalation MRL of 2 ppm for ethylbenzene based on a BMCL for auditory threshold shifts observed in rats exposed to ethylbenzene 6 hours/day, 6 days/week for 4–13 weeks (Gagnaire et al. 2007). The BMCL was estimated using an internal dose metric to simulate time averaged arterial blood concentration of ethylbenzene; a HEC of the BMCL was estimated using a human PBPK model. This $BMCL_{HEC}$ of 63.64 ppm divided by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.06 ppm for ethylbenzene based on a LOAEL for a significant increase in the severity of nephropathy in female rats exposed to ethylbenzene by inhalation for 6 hours/day, 5 days/week for 104 weeks (NTP 1999). Using a PBPK model, an internal dose metric (time averaged arterial blood concentration of ethylbenzene, MCA) of the LOAEL of 75 ppm was simulated. The HEC of this $LOAEL_{MCA}$ (17.45 ppm) was divided an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation with dosimetric adjustment, and 10 for human variability).

The EPA inhalation reference concentration (RfC) (verified in 1991) for ethylbenzene is 1 mg/m^3 (equivalent to 0.23 ppm), based on developmental toxicity seen in rats and rabbits exposed to 4,340 mg/m^3 (Hardin et al. 1981; IRIS 2007; NIOSH 1981).

ATSDR has derived an intermediate-duration oral MRL of 0.4 mg/kg/day for ethylbenzene based on a BMDL for hepatotoxicity (centrilobular hepatocyte hypertrophy) in male rats exposed to ethylbenzene by

gavage for 13 weeks (Mellert et al. 2007). The BMDL was estimated using an internal dose metric to simulate time averaged liver concentrations of ethylbenzene; a HED of the BMDL was estimated using a human PBPK model. This $BMDL_{HED}$ of 10.68 mg/kg/day was divided by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability).

The EPA oral reference dose (RfD) for ethylbenzene is 0.1 mg/kg/day, based on the LOAEL for liver and kidney toxicity in rats administered 291 mg/kg/day ethylbenzene via gavage 5 days/week for 182 days (Wolf et al. 1956). The RfD was calculated by dividing the NOAEL of 97 mg/kg/day by an uncertainty factor of 1,000 (10 for use of a subchronic study, 10 for interspecies extrapolation, and 10 for intraspecies variability).

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

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

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2006
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	0.3 mg/L[b]	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	100 ppm	ACGIH 2006
	STEL (15-minute TWA)	125 ppm	
EPA	AEGL-1, -2, -3	No data	EPA 2007a
	Hazardous air pollutant	Yes	EPA 2007c 42 USC 7412
NIOSH	REL (10-hour TWA)	100 ppm	NIOSH 2005
	STEL (15-minute TWA)	125 ppm	
	IDLH	800 ppm	
OSHA	PEL (8-hour TWA) for general industry	100 ppm	OSHA 2006c 29 CFR 1910.1000
	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
	Designated as a toxic pollutant pursuant to Section 307(a)(1) of the Clean Water Act	Yes	EPA 2007g 40 CFR 401.15
	Drinking water standards and health advisories		EPA 2006a
	1-Day health advisory for a 10-kg child	30 mg/L	
	10-Day health advisory for a 10-kg child	3 mg/L	
	DWEL	3 mg/L	
	Lifetime	0.7 mg/L	
	10^{-4} Cancer risk	No data	

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	National primary drinking water standards		EPA 2003
	MCLG	0.7 mg/L	
	MCL	0.7 mg/L[c]	
	Public health goal	0.7 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	1,000 pounds	EPA 2007d 40 CFR 117.3
	Water quality criteria for human health consumption of:		EPA 2006b
	Water + organism	0.53 mg/L	
	Organism only	2.1 mg/L	
c. Food			
EPA	Inert pesticide ingredients in pesticide products	List 2[d]	EPA 2004
FDA	Bottled water requirement	0.7 mg/L	FDA 2006a 21 CFR 165.110
	EAFUS	No data	FDA 2007b
d. Other			
ACGIH	Carcinogenicity classification	A3[e]	ACGIH 2006
	Biological exposure indices (end of shift at end of workweek); sum of mandelic acid and phenyl glyoxylic acid in urine	1.5 g/g creatinine[f]	
EPA	Carcinogenicity classification	Class D[g]	IRIS 2007
	Oral slope factor	No data	
	Inhalation unit risk	No data	
	RfC	1 mg/m^3	
	RfD	0.1 mg/kg/day	
	Master Testing List	Yes[h]	EPA 2007j
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes[i]	EPA 2007e 40 CFR 302.4
	Reportable quantity	1,000 pounds	
	Effective date of toxic chemical release reporting	01/01/87	EPA 2007f 40 CFR 372.65
	TSCA health and safety data reporting requirements	Yes	EPA 2007h 40 CFR 716.120

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
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.
[c]Potential health effects from exposure above the MCL include liver or kidneys problems; and the common sources of contaminant in drinking water is from the discharge from petroleum refineries.
[d]List 2: potentially toxic other ingredients and high priority for testing inerts
[e]A3: confirmed animal carcinogen with unknown relevance to humans
[f]ACGIH (2006) has submitted notice of intended changes for ethylbenzene in which the BEI will be lowered to 0.7 g/g creatinine.
[g]Class D: not classifiable as to human carcinogenicity
[h]Ethylbenzene was recommended to the Master Testing List (MTL) by the U.S. EPA's Office of Pollution Prevention and Toxics on the basis of the Screening Information Data Sets (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. The Office of Air and Radiation recommended ethylbenzene to the MTL in 1995 on the basis that ethylbenzene is a hazardous air pollutant. EPA is in the process of determining the testing needs for the following: acute toxicity, neurotoxicity, developmental toxicity, reproductive, and immunotoxicity
[i]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) and Section 307(a) of the Clean Water and Section 112 of the Clean Air Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Levels; BEI = biological exposure indices; 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; FDA = Food and Drug Administration; 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; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term expsoure limit; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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: Ethylbenzene
CAS Numbers: 100-41-4
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

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

Reference: Cappaert NLM, Klis SFL, Baretta AB, et al. 2000. Ethyl benzene-induced ototoxicity in rats: A dose-dependent mid-frequency hearing loss. J Assoc Res Otolaryngol 1(4):292-299.

Experimental design: Wag/Rij rats (8 rats/group; sex not provided) were exposed to 0, 300, 400, or 550 ppm ethylbenzene (99% pure) 8 hours/day for 5 days. Animal weight was recorded weekly. Measurement of Distortion Product Otoacoustic Emissions (DPOAE), Compound Action Potential (CAP), and hair cell counts were conducted 3–6 weeks after the last ethylbenzene exposure.

DPOAE: Stimuli were delivered to the ear canal via a probe system incorporating two speakers and a low-noise microphone. The microphone signal was amplified and the response to the stimulus was measured. DPOAE amplitude growth curves with stimulus levels were obtained from both ears. Growth functions were obtained at 4, 5.6, 8, 11.3, 16, and 22.6 kHz. The DPOAE threshold, defined as the stimulus level required to elicit a response of 0 dB SPL DPOAE was determined for each of the six frequencies.

CAP: CAP was conducted immediately after DPOAE measurements. Auditory-evoked responses were recorded via a silverball electrode at the apex of the cochlea after presenting tone bursts of 1, 2, 4, 8, 12, 16, and 24 kHz. An isoresponsive criterion of 1 μV level was used to define CAP thresholds. CAP amplitude was defined as the difference between the first negative peak and the summating potential in the electrophysiologic response. Hair cell counts: Immediately after conducting the electrocochleography (CAP) cochleas were removed and bisected longitudinally. Hair cell counts were conducted on five locations of the organ of Corti. Outer hair cell (OHC) loss was determined and expresses as a percentage of the expected number of OHC in different auditory regions.

Effect noted in study and corresponding doses: Rats did not show signs of ill health. There were no significant differences in terminal body weight between exposed and control rats.

DPOAE: DPOAE amplitude growth curves showed a significant reduction in rats exposed to 550 ppm, but not 300 or 400 ppm ethylbenzene. Effects were significant at 5.6, 8, and 11.3 kHz, but not at other frequencies. The DPOAE thresholds were significantly shifted (increased stimulus was needed to elicit the threshold response) at 5.6, 8, 11.3, and 16 kHz in rats in the 550-ppm group. DPOAE threshold shifts were not observed in other exposure groups.

CAP: Animals exposed to 550 ppm showed a significant shift in the CAP amplitude growth curves at 8, 12, and 16 kHz. In the 400-ppm group, the growth curves were affected only at 12 kHz and there was no effect in animals in the 300-ppm group. CAP thresholds were significantly shifted at 8, 12, and 16 kHz in the 550-ppm group and at 12 and 16 kHz in the 400-ppm group. There was no deterioration of CAP thresholds in the 300-ppm group. Significant OHC losses of approximately 33 and 75% were observed in

the 550-ppm group in the auditory regions corresponding to 11 and 21 kHz, respectively. In the 400-ppm group, significant losses (25%) were observed in the 11 kHz region. OHC losses in the 21 kHz region in the 300-ppm group were approximately 12%, but were not statistically significant.

Dose and end point used for MRL derivation: $BMCL_{1SD}$ of 81.10 μmol/L for CAP auditory shifts using an internal dose metric of time-averaged arterial blood concentration of ethylbenzene.

[] NOAEL [ ] LOAEL [x] BMCL

The point of departure for an acute-duration inhalation MRL was identified using BMD analysis of the CAP auditory threshold data from the Cappaert et al. (2000) study. The data were presented graphically in the paper; however, Dr. Cappaert provided individual animal data for the CAP thresholds (presented in Figures 3 and 4 in the published paper) to ATSDR (data on OHC loss were not available). Data from Figure 4 included measurements of CAP thresholds in response to auditory stimuli ranging from 1 to 24 kHz. The largest effects on CAP threshold occurred in response to 8, 12, and 16 kHz stimuli and, on this basis, these data were selected for BMD modeling. The raw data set from Dr. Cappaert was used to make the following calculations:

1. *Control group mean (±SD) CAP threshold*: mean CAP stimulus threshold (dB SPL, defined as ≥1 μV CAP) of control group;

2. *Individual animal threshold shift in response to ethylbenzene exposure*: mifference between threshold for each animal exposed to ethylbenzene and the control group mean threshold; and

3. *Ethylbenzene exposure group mean (±SD) threshold shift*: mean (±SD) of individual threshold shifts for each ethylbenzene exposure group. These group mean responses (mean CAP threshold shift, dB) were used as the response metric in BMD modeling.

Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001) (see Appendix E for additional information on the PBPK model). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure concentrations ranging from 1 to 50 ppm. For cochlear effects, the assumption was made that ethylbenzene, rather than a metabolite, is the toxic agent. Although there are no data for ethylbenzene, support of this assumption comes from studies of toluene (Pryor et al. 1991) and styrene (Ladefoged et al. 1998), which found that ototoxicity was most likely due to the action of the parent compound rather than a metabolite. The dose metric simulated for the cochlear effects was time-averaged arterial blood concentration of ethylbenzene (MCA) because there are no validated models for simulating ethylbenzene levels in cochlea tissue or enodolymph. Using MCA for this end point assumes that tissue dosimetry and response would be correlated with time averaged arterial ethylbenzene concentrations (or average x time, AUC), which would be expected to correlate with time-averaged tissue concentration.

The CAP threshold shift data (summarized in Table A-1) were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.1.1) using MCA as the dose metric. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual

at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. If the test for constant variance was negative, then the linear model was run again while applying the power model integrated into BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For all models, a BMR of 1 standard deviation change from the control was used. This default BMR was used because there are insufficient mechanism of action data to determine what level of response constitutes a biologically significant effect in the cochlea.

Table A-1. CAP Threshold Shifts in Wag/Rij Rats Exposed to Ethylbenzene 8 Hours/Day for 5 Days

Frequency (kHz)	Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (dB)	SD	Number of rats
8					
	0	0	0.00	5.66	7
	300	76.11	-3.45	11.09	8
	400	119.00	4.36	9.94	7
	550	198.10	23.93	6.11	8
12					
	0	0	0.00	6.30	7
	300	76.11	-3.51	11.31	8
	400	119.00	14.79	9.53	7
	550	198.10	30.62	5.78	8
16					
	0	0	0.00	7.18	7
	300	76.11	-0.35	10.43	8
	400	119.00	15.57	12.00	7
	550	198.10	21.84	7.37	8

CAP = compound action potential; MCA = time-averaged arterial blood concentration of ethylbenzene; SD = standard deviation

Source: Cappaert et al. 2000

The model predictions for CAP threshold shifts at 8, 12, and 16 kHz are summarized in Table A-2. At the 8 kHz frequency, the Hill, polynomial (2- and 3-degree), and power models provided adequate fit to the data. Of these models, the polynomial (3-degree) model (Figure A-1) had the lowest AIC. At 12 and 16 kHz frequencies, only the Hill model provided an adequate fit to the data; the models are presented in Figures A-2 and A-3.

Table A-2. Model Predictions for CAP Threshold Shifts in Wag/Rij Rats Exposed to Ethylbenzene 8 Hours/Day for 5 Days

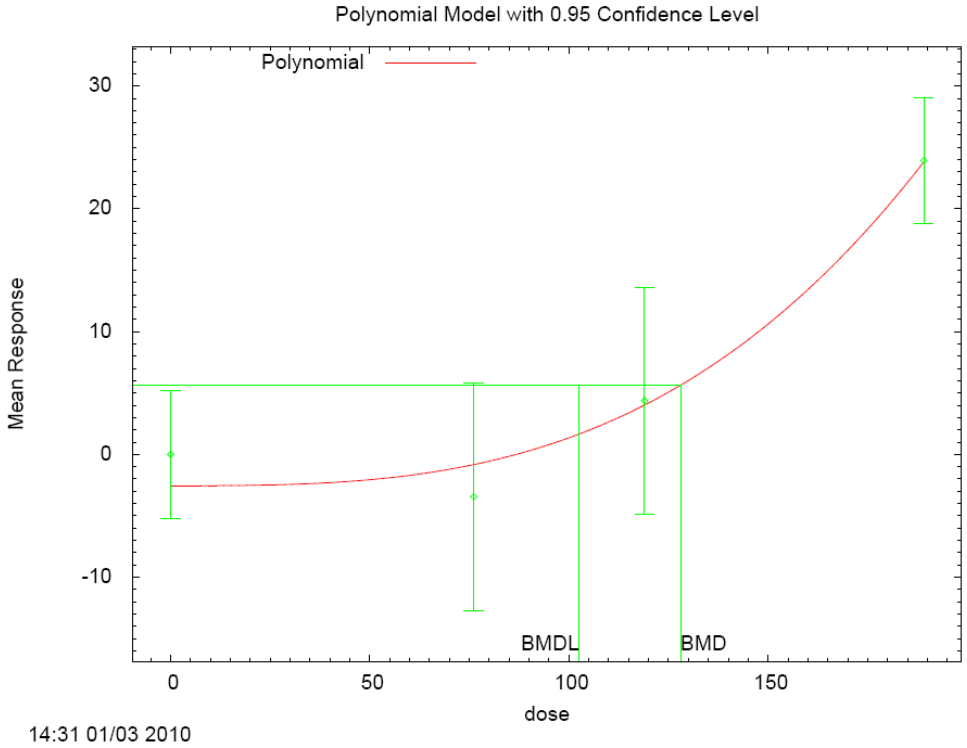
Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
8 kHz frequency					
Constant variance					
Hill[b]	0.17	0.41	163.26	121.43	104.55
Linear[c]	0.17	0.00	174.14	NA	NA
Polynomial (2-degree)[b]	0.17	0.14	164.53	105.93	91.96
Polynomial (3-degree)[b]	**0.17**	**0.46**	**162.12**	**128.00**	**102.63**
Power[b]	0.17	0.24	163.94	136.36	101.61
12 kHz frequency					
Constant variance					
Hill[b]	**0.19**	**0.40**	**163.36**	**111.59**	**89.47**
Linear[c]	0.19	0.00	176.02	NA	NA
Polynomial (2-degree)[b]	0.19	0.03	167.42	NA	NA
Polynomial (3-degree)[b]	0.19	0.01	169.42	NA	NA
Power[b]	0.19	0.01	169.32	NA	NA
16 kHz frequency					
Constant variance					
Hill[b]	**0.42**	**0.94**	**168.39**	**110.51**	**81.10**
Linear[c]	0.42	0.04	172.72	NA	NA
Polynomial (2-degree)[b]	0.42	0.03	173.35	NA	NA
Polynomial (3-degree)[b]	0.42	0.03	173.35	NA	NA
Power[b]	0.42	0.03	173.12	NA	NA

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

AIC = Akaike Information Criterion; BMC = benchmark concentration associated with a 1 standard deviation benchmark response; BMCL = 95% lower confidence limit on the BMC; CAP = compound action potential; NA = not applicable, model does not provide adequate fit to the data

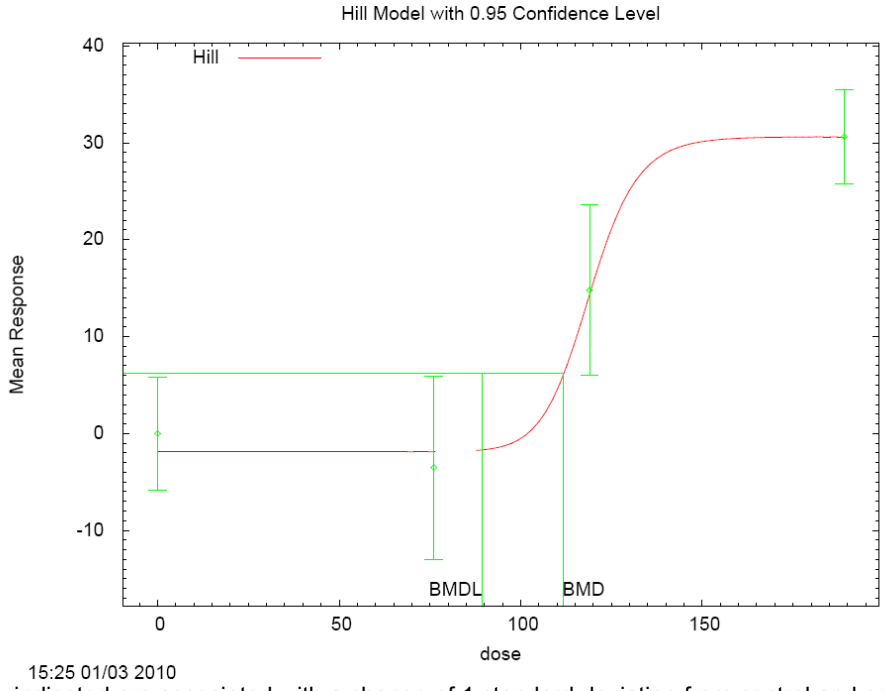
Source: Cappaert et al. 2000

Figure A-1. Predicted (3-Degree Polynomial Model with Constant Variance) and Observed CAP Threshold Shifts at 8 kHz *



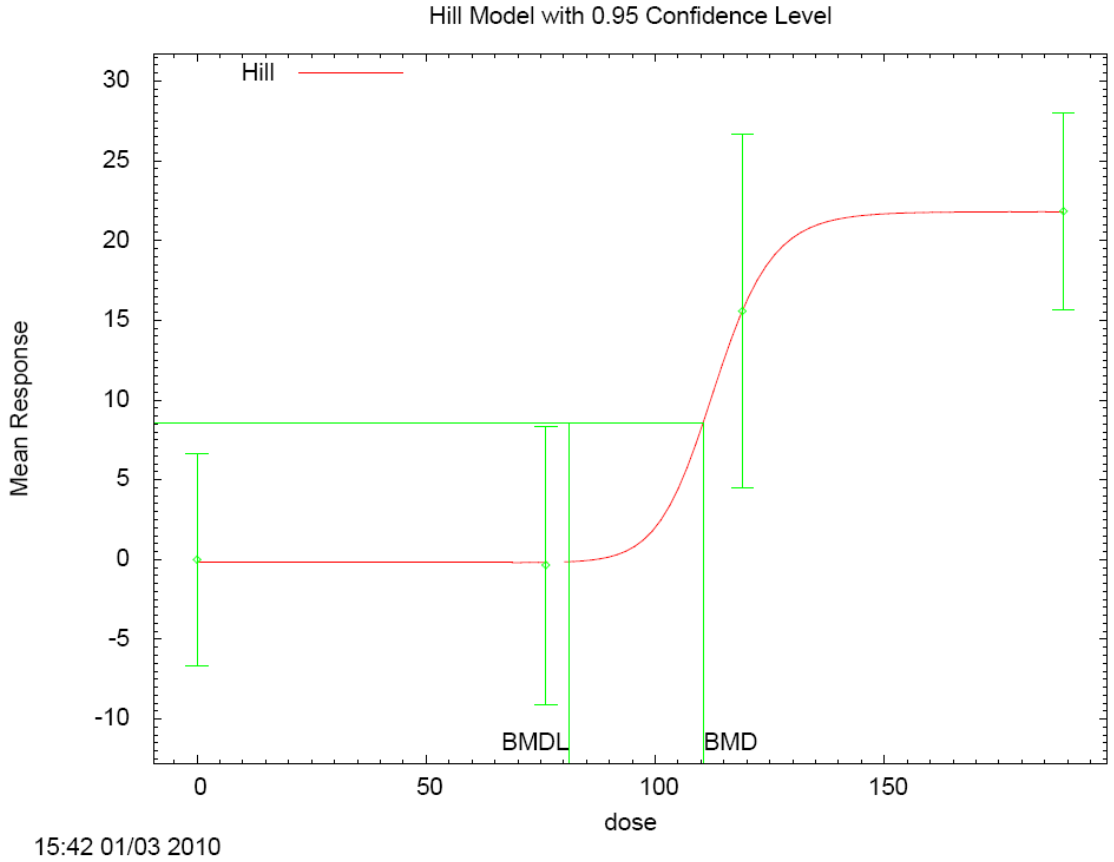
*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

Figure A-2. Predicted (Hill Model with Constant Variance) and Observed CAP Threshold Shifts at 12 kHz*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

Figure A-3. Predicted (Hill Model with Constant Variance) and Observed CAP Threshold Shifts at 16 kHz*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

The $BMDL_{1SD}$ values estimated from the BMD model with the lowest AIC for CAP threshold data at 8, 12, and 16 kHz were 102.3, 89.47, and 81.10 µmol/L, respectively. The lowest $BMDL_{1SD}$ of 81.10 µmol/L was selected as the point of departure.

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: HECs were predicted from the $BMCL_{1SD}$ values (estimated from the model with the lowest AIC values) for CAP threshold data at 8, 12, and 16 kHz using the human PBPK model. The BMCL values for the internal dose metric (MCA) were converted to HEC values by iterative simulation of human inhalation exposures. Exposure concentrations were varied until the simulated value for the internal dose metric was within 0.01% of the BMCL. The HECs for $BMCL_{1SD}$ values are presented in Table A-3.

Table A-3. Human Equivalent Concentrations (HECs) for CAP Threshold Shifts

Effect	Model	$BMCL_{1SD}$ (µmol/L)	HEC[a] (ppm)
CAP threshold shift at 8 kHz	Polynomial (3-degree)	102.63	178.52
CAP threshold shift at 12 kHz	Hill	89.47	163.80
CAP threshold shift at 16 kHz	Hill	81.10	154.26

[a]Calculated using a reference human body weight of 70 kg and the assumption of 14-day continuous exposure.

$BMCL_{MCA}$ = 95% lower confidence limit on the benchmark concentration associated with a benchmark response of 1 standard deviation estimated using an MCA (time-weighted arterial blood concentration of ethylbenzene) dose metric; CAP = compound action potential

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HECs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: There is limited information on the acute toxicity of ethylbenzene in humans. Acute exposures to ≥1,000 ppm resulted in ocular irritation, a burning sensation, and profuse lacrimation (Cometto-Muniz and Cain 1995; Thienes and Haley 1972; Yant et al. 1930). Volunteers exposed to 2,000 ppm reported irritation and chest constriction with worsening symptoms when the concentration was increased to 5,000 ppm (Yant et al. 1930). Studies in laboratory animals identify ototoxicity as the most sensitive end point for acute-duration inhalation exposure to ethylbenzene. Damage to the OHCs of the organ of Corti and, in some cases, significant reductions in auditory thresholds were observed in rats exposed to ≥400 ppm ethylbenzene by inhalation for 5 days (Cappaert et al. 1999, 2000, 2001, 2002). Loss of OHCs appeared to be concentration-related as losses were 52–66% in animals exposed to 800 ppm ethylbenzene (Cappaert et al. 1999), 40–75% at 550 ppm, and approximately 25% at 400 ppm (Cappaert et al. 2000, 2001). OHC losses in rats exposed to 300 ppm were small (12%) and not statistically significant (Cappaert et al. 2000). Auditory thresholds in rats exposed to ethylbenzene at ≥400 ppm were significantly affected in the mid-frequency region; however, an increasingly broader range of frequencies were affected with increasing concentrations of ethylbenzene (Cappaert et al. 1999, 2000). Auditory assessments indicate that effects were evident shortly after exposure and persisted for up to 11 weeks (termination of the observation period) (Cappaert et al. 1999, 2000, 2001, 2002), suggesting that the auditory effects might be irreversible. Cappaert et al. (2002) demonstrated a significant species difference in the susceptibility of rats and guinea pigs to the ototoxic effects of ethylbenzene with guinea pigs showing no auditory deficits or losses in OHCs at 2,500 ppm ethylbenzene after 5 days (Cappaert et al. 2002).

Neurological effects were observed after acute-duration exposure to ethylbenzene at concentrations equal to or higher than those that elicited auditory effects in animals. Effects observed after acute-duration exposure to ethylbenzene include moderate activation of motor behavior in rats exposed to 400 ppm (Molnar et al. 1986) and reduced activity and prostration and shallow breathing in rats and mice at 1,200 ppm (Ethylbenzene Producers Association 1986a). Rats or mice exposed to ≥2,000 ppm showed posture changes, reduced grip strength, reduced motor coordination (Tegeris and Balster 1994), narcotic effects (Molnar et al. 1986), and neurotransmission disturbances in the forebrain and hypothalamus (Andersson et al. 1981). Mice exposed to 4,060 ppm for 20 minutes showed a 50% reduction in respiratory rate (Nielsen and Alarie 1982). A 50% respiratory depression observed in mice at 1,432 ppm was attributed to sensory irritation (De Ceaurriz et al. 1981).

Increased liver weight was reported after acute-duration exposure in rats exposed to ≥400 ppm ethylbenzene (Ethylbenzene Producers Association 1986a; Toftgard and Nilsen 1982), but not in mice at 1,200 ppm or rabbits at 2,400 ppm (Ethylbenzene Producers Association 1986a). At these same levels and exposure durations, induction of microsomal enzymes and related ultrastructural changes (e.g., proliferation of the smooth endoplasmic reticulum) were observed. These effects occurred in the absence of histopathological changes to the liver. Therefore, the effects on the liver appear to be related to induction of microsomal enzymes in smooth endoplasmic reticulum. An increase in relative kidney weight was also observed in rats exposed to ≥1,200 ppm (Ethylbenzene Producers Association 1986a; Toftgard and Nilsen 1982), but not in mice at 1,200 ppm or rabbits at 2,400 ppm (Ethylbenzene Producers Association 1986a). However, increased kidney weights occurred in the absence of histological changes (Ethylbenzene Producers Association 1986a). No histopathological alterations were observed in the lungs of surviving rats, mice, or rabbits exposed to 1,200, 400, or 2,400 ppm ethylbenzene, respectively, for 4 days (Ethylbenzene Producers Association 1986a).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, Heraline Hicks

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 42
Species: Rat

Minimal Risk Level: 2 [ ] mg/kg/day [x] ppm

Reference: Gagnaire F, Langlais C, Grossman S, et al. 2007. Ototoxicity in rats exposed to ethylbenzene and to two xylene vapors for 13 weeks. Arch Toxicol 81:127-143.

Experimental design: Male Sprague-Dawley rats (14 rats/exposure group) were exposed to 0, 200, 400, 600 and 800 ppm ethylbenzene (99% pure), 6 hours/day, 6 days/week, for 13 weeks. Ototoxicity was assessed based on effects on neurophysiological measurements and cochlear total hair cell counts. For the neurophysiologic assessments, rats were surgically fitted with electrodes (active electrode was placed at the lamba point over the inferior colliculus, the reference electrode was placed posterior to the bregma and to the right of the midline, and the ground electrode was placed over the nasal bone). Exposure to ethylbenzene was conducted starting 3–4 weeks after implantation of the electrodes and neuro-physiological measurements were conducted at the end of 4th, 8th, and 13th week of exposure and at the end of the 8th week of recovery (week 21). Brainstem auditory responses were evoked with 50 microsecond clicks at 10 clicks/second presented in 5 dB steps. The evoked activity was analyzed for 10 ms following each click. Audiometric thresholds were determined at 2, 4, 8, and 16 kHz by inspection of the auditory brainstem responses. Following the 8th week of recovery (post-exposure) eight rats/group were sacrified. The organ of Corti and the basilar membrane were dissected from the cochlea and prepared for total hair cell counts (cytocochleograms). Four left and four right cochleas were prepared in this manner in all groups including controls.

Effect noted in study and corresponding doses: In the 800 ppm group, one rat lost its head plug and could not undergo neurophysiological testing, one rat died for unknown reasons and another rat was sacrificed due to a large neck tumor. There were no significant differences in body weight gain between the surviving treated animals and controls.

Audiometric thresholds at 2, 4, 8, and 16 kHz were significantly higher in animals exposed to 400, 600, and 800 ppm ethylbenzene than in controls ($p<0.05$). The effect was evident at week 4, did not increase significantly throughout the exposure period, and was not reversed after 8 weeks of recovery. No shift in audiometric thresholds was observed in rats in the 200 ppm group.

The morphological assessment of the organ of Corti (conducted after an 8-week recovery period) showed significant losses (up to 30% of the OHC in the mid frequency region) in the third row of the OHC in 4/8 rats exposed to 200 ppm. A dose related loss in third row OHC (OHC3) was evident with almost complete loss observed in the 600- and 800-ppm groups. The data suggest that the extent of the damage at each dose was greatest in the OHC3 followed, in decreasing order, by damage in OHC2, OHC1, and inner hair cells (IHC). There was no significant hair loss in the control animals. The LOAEL for OHC3 loss was 200 ppm. A NOAEL was not established.

Dose and end point used for MRL derivation: $BMDL_{1SD}$ of 19.94 µmol/L for auditory shifts using an internal dose metric of time-averaged arterial blood concentration of ethylbenzene.

[] NOAEL [ ] LOAEL [x] BMCL

Auditory threshold shifts and OHC loss are selected as the critical effects following intermediate-duration inhalation exposure to ethylbenzene. Because these data are only presented graphically in the Gagnaire's paper, the data are not suitable for BMD analysis. However, Dr. Gagnaire has provided to ATSDR the individual animal data for these end points; these data are summarized in Tables A-4 and A-5.

Table A-4. Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 or 13 Weeks

Frequency (kHz)	Exposure duration (weeks)	Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (dB SPL)	SD	Number of rats
4						
	4					
		0	0	33	4	14
		200	20.97	31	4	13
		400	64.26	52	11	14
		600	118.07	75	7	14
		800	177.98	74	6	14
	13					
		0	0	31	4	14
		200	20.97	31	5	13
		400	64.26	59	8	14
		600	118.07	74	8	14
		800	177.98	73	7	14
8						
	4					
		0	0	22	4	14
		200	20.97	23	5	13
		400	64.26	40	11	14
		600	118.07	69	8	14
		800	177.98	68	6	14
	13					
		0	0	22	4	14
		200	20.97	21	4	13
		400	64.26	44	15	14
		600	118.07	71	9	14
		800	177.98	67	7	14

Table A-4. Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 or 13 Weeks

Frequency (kHz)	Exposure duration (weeks)	Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (dB SPL)	SD	Number of rats
16						
	4					
		0	0	21	3	14
		200	20.97	20	4	13
		400	64.26	40	16	14
		600	118.07	70	6	14
		800	177.98	68	5	14
	13					
		0	0	18	3	14
		200	20.97	18	4	13
		400	64.26	46	18	14
		600	118.07	74	9	14
		800	177.98	67	7	14

MCA = time-averaged arterial blood concentration of ethylbenzene; SD = standard deviation; SPL = sound pressure level

Source: Gagnaire et al. 2007

Table A-5. Percent OHC Loss in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 13 Weeks[a]

Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (% loss)	SD	Number of rats
0	0	0.346	0.159	7
200	20.97	3.67	4.24	8
400	64.26	67.12	12.26	8
600	118.07	85.58	7.68	8
800	177.98	90.81	7.36	8

[a]Evaluation conducted at the end of the 8-week recovery period.

MCA = time-averaged arterial blood concentration of ethylbenzene; OHC = outer hair cell; SD = standard deviation

Source: Gagnaire et al. 2007

Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001) (see Appendix E for additional information on the PBPK model). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure

concentrations ranging from 1 to 50 ppm. For cochlear effects, the assumption was made that ethylbenzene, rather than a metabolite, is the toxic agent. Although there are no data for ethylbenzene, support of this assumption comes from studies of toluene (Pryor et al. 1991) and styrene (Ladefoged et al. 1998), which found that ototoxicity was most likely due to the action of the parent compound rather than a metabolite. The dose metric simulated for the cochlear effects was time-averaged arterial blood concentration of ethylbenzene (MCA) because there are no validated models for simulating ethylbenzene levels in cochlea tissue or endolymph. Using MCA for this endpoint assumes that tissue dosimetry and response would be correlated with time averaged arterial ethylbenzene concentrations (or average x time, AUC), which would be expected to correlate with time-averaged tissue concentration.

For the BMD analysis, the auditory threshold and percent OHC loss data were fit to all available continuous models in EPA's BMDS (version 2.1.1) using MCA as the dose metric. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For data sets that did not provide an adequate fit to the available models, the highest or two highest doses were dropped and the models were fit to the modified data set. ATSDR considered this an acceptable procedure because the BMD modeling was used to predict the response at low doses. For all models, a BMR of 1 standard deviation change from the control was used. This default BMR was used because there are insufficient mechanism of action data to determine what level of response constitutes a biologically significant effect in the cochlea.

The model predictions for auditory threshold after 4 and 13 weeks of exposures are presented in Tables A-6 and A-7. None of the BMD models provided an adequate fit (as assessed by the goodness-of-fit criteria) to the OHC loss data.

Table A-6. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
4 kHz frequency					
All doses					
Constant variance					
Linear[b]	0.0004	<0.0001	382.99	NA	NA
Nonconstant variance					
Linear[b]	0.002	<0.0001	435.85	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	0.0002	0.0001	286.70	NA	NA
Nonconstant variance					
Linear[b]	0.007	<0.0001	312.35	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.001	216.31	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.66	<0.0001	207.43	NA	NA
Polynomial (2-degree)[c]	0.66	0.010	194.79	NA	NA
Power[c]	**0.66**	**0.21**	**189.65**	**58.75**	**33.12**
8 kHz frequency					
All doses					
Constant variance					
Linear[b]	0.002	<0.0001	387.55	NA	NA
Nonconstant variance					
Linear[b]	0.004	<0.0001	438.09	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	0.001	0.002	291.87	NA	NA
Nonconstant variance					
Linear[b]	0.02	<0.0001	392.73	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	0.0003	0.05	211.83	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output; the number of observations				

Table A-6. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
were less than the number of parameters for the Hill model					
Linear[b]	0.61	0.01	200.49		
Polynomial (2-degree)[c]	**0.61**	**0.69**	**194.10**	**30.34**	**19.94**
Power[c]	0.61	NA	195.94	NA	NA
16 kHz frequency					
All doses					
Constant variance					
Linear[b]	<0.0001	<0.0001	404.82	NA	NA
Nonconstant variance					
Linear[b]	<0.0001	<0.0001	447.85	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	<0.0001	0.002	310.22	NA	NA
Nonconstant variance					
Linear[b]	<0.0001	<0.0001	315.43	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.03	235.61	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.20	0.00	203.91	NA	NA
Polynomial (2-degree)[c]	0.20	0.07	195.17	NA	NA
Power[c]	**0.20**	**0.84**	**191.99**	**58.34**	**27.31**

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

AIC = Akaike Information Criterion; BMC = benchmark concentration associated with a benchmark response of 1 standard deviation; BMCL = 95% lower confidence limit on the BMC; NA = not applicable, model failed to provide an adequate fit to the data; SD = standard deviation

Source: Gagnaire et al. 2007

Table A-7. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 13 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
4 kHz frequency					
All doses					
Constant variance					
Linear[b]	0.05	<0.0001	385.41	NA	NA
Nonconstant variance					
Hill[c]	**0.64**	**0.93**	**322.34**	**54.91**	**28.59**
Linear[b]	0.64	<0.0001	437.05	NA	NA
Polynomial (2-degree)[c]	0.64	0.0001	419.18	NA	NA
Polynomial (3-degree)[c]	0.64	<0.0001	419.88	NA	NA
Polynomial (4-degree)[c]	0.64	<0.0001	414.64	NA	NA
Power[c]	0.64	<0.0001	375.90	NA	NA
8 kHz frequency					
All doses					
Constant variance					
Linear[b]	<0.0001	<0.0001	408.00	NA	NA
Nonconstant variance					
Linear[b]	<0.0001	<0.0001	447.64	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	<0.0001	0.01	310.79	NA	NA
Nonconstant variance					
Linear[b]	0.001	<0.0001	402.37	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.01	233.73	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output, the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.78	<0.0001	213.91	NA	NA
Polynomial (2-degree)[c]	0.78	0.03	201.59	NA	NA
Power[c]	**0.78**	**0.54**	**197.02**	**58.29**	**29.71**
16 kHz frequency					
All doses					
Constant variance					
Linear[b]	<0.0001	<0.0001	434.87	NA	NA
Nonconstant variance					

Table A-7. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 13 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
Linear[b]	<0.0001	<0.0001	474.46	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	<0.0001	0.03	322.19	NA	NA
Nonconstant variance					
Linear[b]	0.0001	<0.0001	416.55	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.01	245.83	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output, the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.34	<0.0001	211.61	NA	NA
Polynomial (2-degree)[c]	0.34	0.06	198.11	NA	NA
Power[c]	0.34	NA	196.52	NA	NA

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

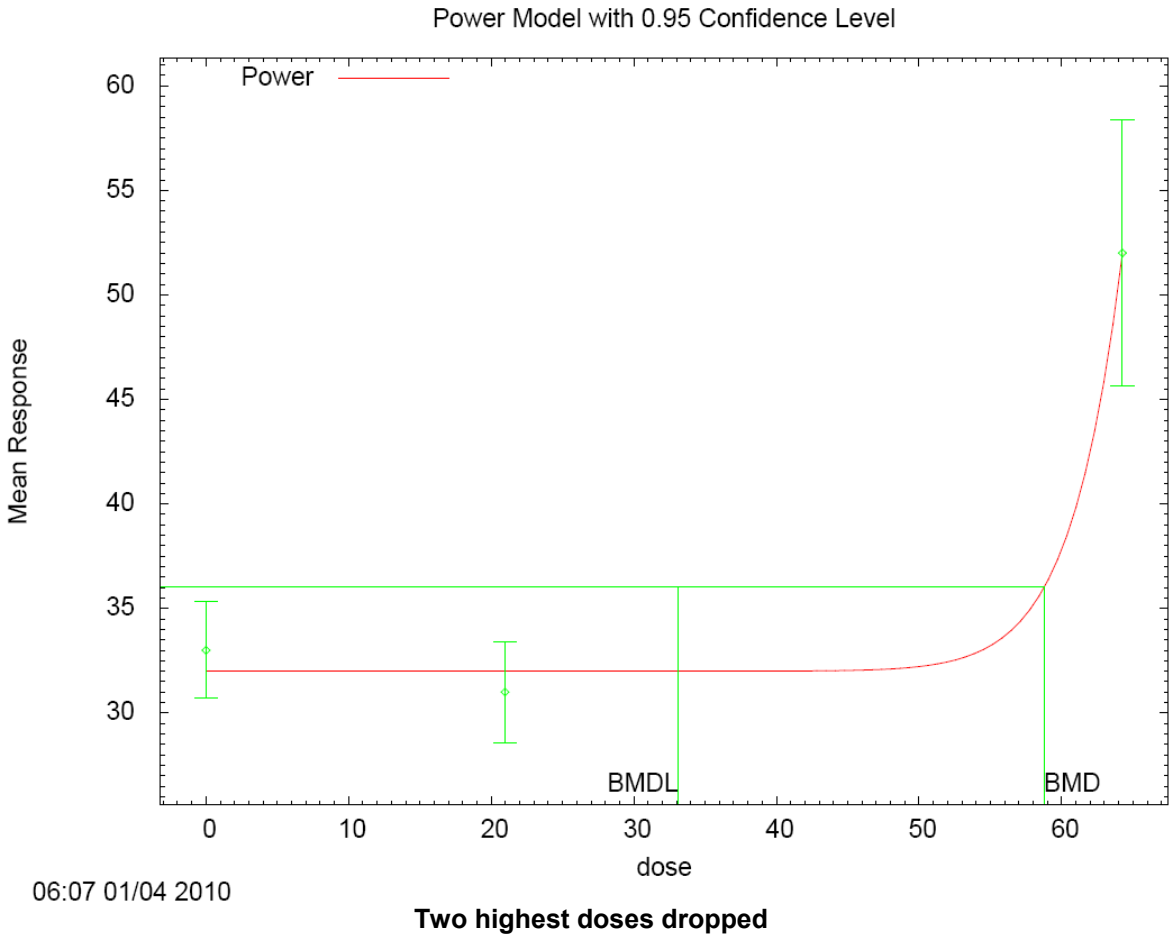
AIC = Akaike Information Criterion; BMC = benchmark concentration associated with a benchmark response of 1 standard deviation; BMCL = 95% lower confidence limit on the BMC; NA = not applicable, model failed to provide an adequate fit to the data; SD = standard deviation

Source: Gagnaire et al. 2007

Most of the available BMDS models did not adequately fit the auditory threshold data; however, with the exception of the auditory thresholds at 16 kHz in rats exposed to ethylbenzene for 13 weeks, one BMD model fit each data set often when the highest two dose groups were dropped. In rats exposed to ethylbenzene for 4 weeks, the power with nonconstant variance, 2-degree polymonial with nonconstant variance, and power models adequately fit the auditory shift data assessed at 4, 8, or 16 kHz, respectively; these models are shown in Figures A-4, A-5, and A-6. The Hill model with nonconstant variance (Figure A-7) and the power model with nonconstant variance (FigureA- 8) adequately fit the auditory threshold shift data assessed at 4 and 8 kHz, respectively, for rats exposed for 13 weeks.

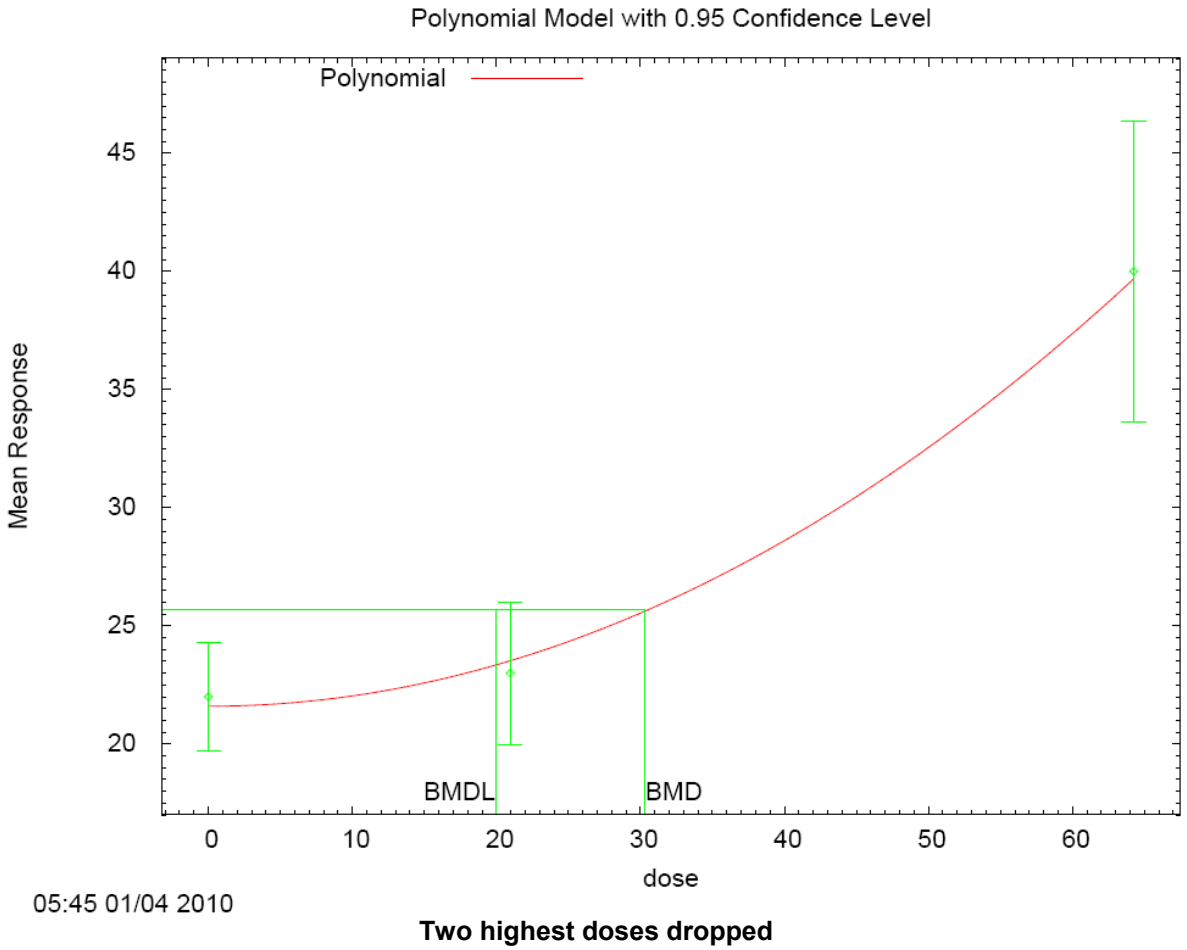
The $BMDL_{1SD}$ values estimated from the BMD model with the lowest AIC for changes in auditory threshold for each frequency and duration ranged from 19.94 to 33.21 µmol/L. Although there is a degree of uncertainty associated with the BMD models in which the two highest doses were dropped, the narrow range of BMCL values estimated from the truncated data sets and the full data set supports this approach. The lowest $BMDL_{1SD}$ of 19.94 µmol/L (estimated using auditory threshold data at 8 kHz following 4 weeks of exposure) was selected as the point of departure.

Figure A-4. Predicted (Power Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 4 kHz (4-Week Exposure)*



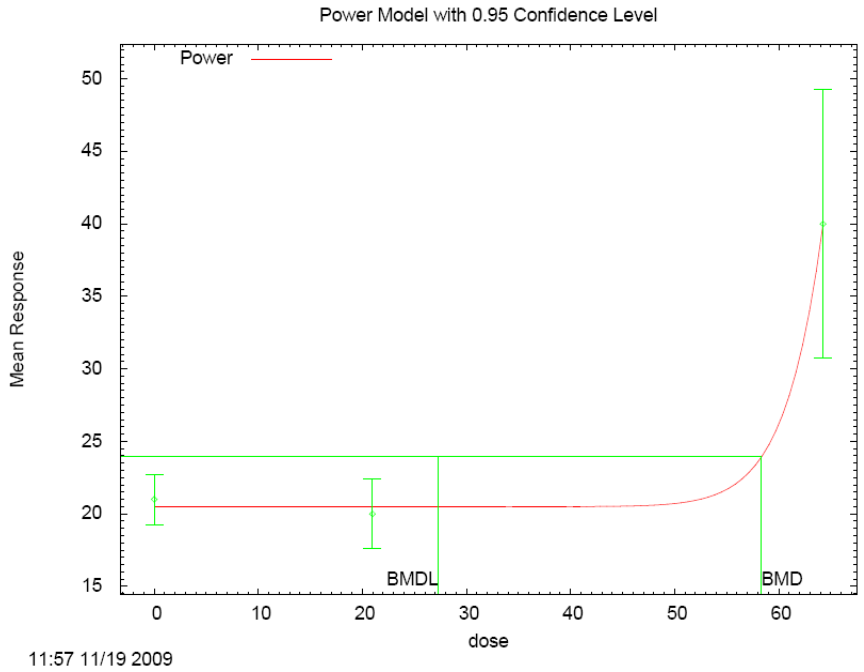
*BMCs and BMCLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

Figure A-5. Predicted (2-Degree Polynomial Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 8 kHz (4-Week Exposure)*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

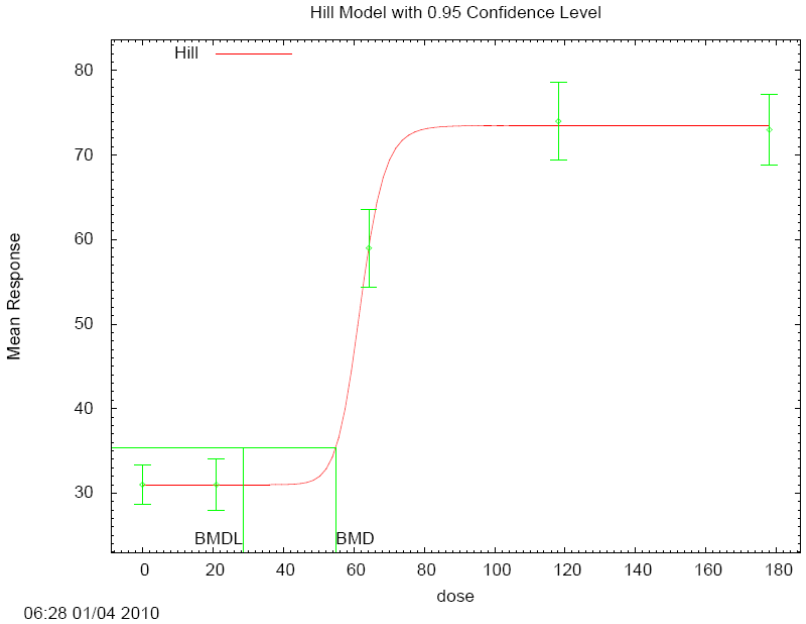
Figure A-6. Predicted (Power Model) and Observed Changes in Auditory Threshold at 16 kHz (4-Week Exposure)*



Two highest doses dropped

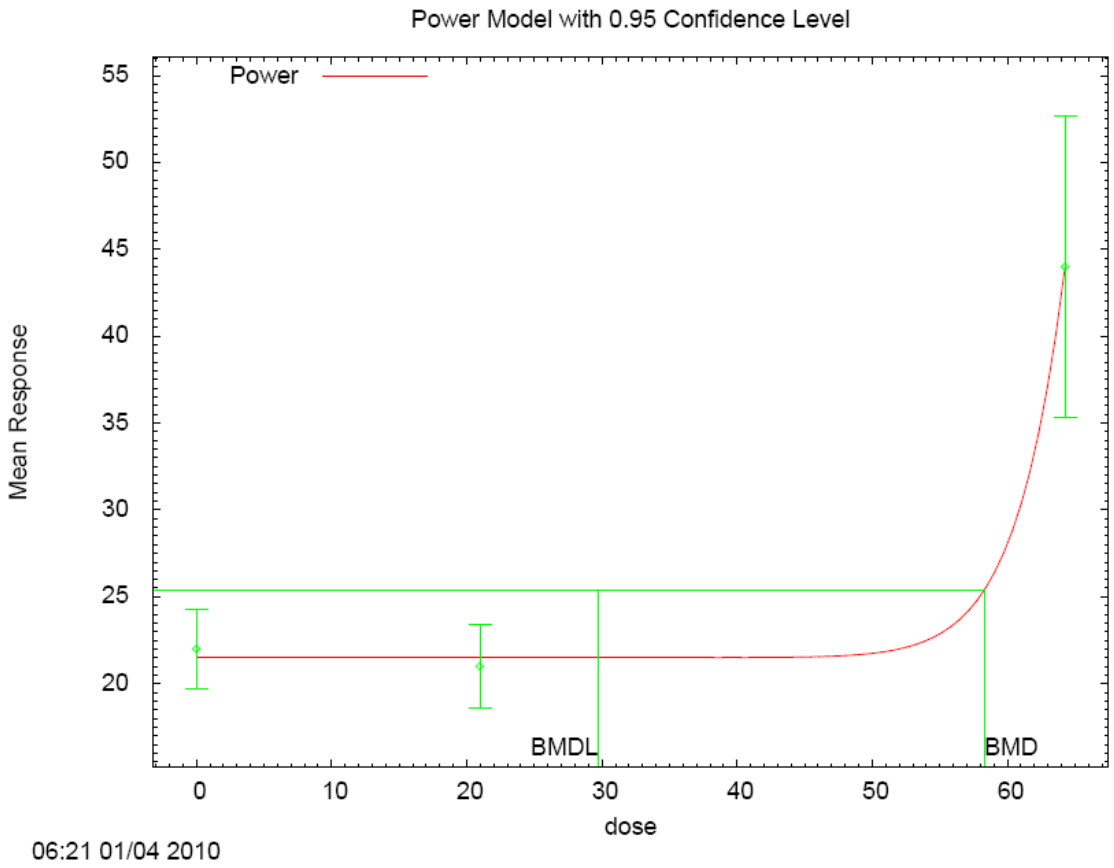
*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

Figure A-7. Predicted (Hill Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 4 kHz (13-Week Exposure)*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

Figure A-8. Predicted (Power Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 8 kHz (13-Week Exposure)*



Two highest doses dropped

*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control and are in units of µmol/L.

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: The human PBPK model was used to predict HECs corresponding to specific BMCL values. The BMCL values for the internal dose metric (MCA) were converted to HEC values by iterative simulation of human inhalation exposures. Exposure concentrations were varied until the simulated value for the internal dose metric was within 0.01% of the BMCL. The HECs for $BMCL_{1SD}$ values estimated from the models providing adequate fit are listed in Table A-8. The HECs of the $BMCL_{1SD}$ values ranged from 63.64 to 87.13 ppm; the lowest HEC of 63.64 ppm was selected as the point of departure for the MRL.

Table A-8. Human Equivalent Concentrations for Auditory Effects in Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 or 13 Weeks

Effect	Model	$BMCL_{MCA}$ µmol/L)	HEC[a] (ppm)
Auditory thresholds at 4 kHz following 4 weeks of exposure	Power (two highest doses dropped); nonconstant variance	33.12	87.13
Auditory thresholds at 8 kHz following 4 weeks of exposure	2-Degree polynomial (two highest doses dropped); nonconstant variance	19.94	63.64
Auditory thresholds at 16 kHz following 4 weeks of exposure	Power (two highest doses dropped); nonconstant variance	27.31	77.77
Auditory thresholds at 4 kHz following 13 weeks of exposure	Hill (all doses); nonconstant variance	28.59	79.95
Auditory thresholds at 8 kHz following 13 weeks of exposure	Power (two highest doses dropped); nonconstant variance	29.71	81.79

[a]Calculated using a reference human body weight of 70 kg and the assumption of 364-day continuous exposure.

$BMCL_{MCA}$ = 95% lower confidence limit on the benchmark concentration associated with a benchmark response of 1 standard deviation estimated using an MCA (time-weighted arterial blood concentration of ethylbenzene) dose metric

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HECs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: Several studies in animals, but no studies in humans, have examined the toxicity of ethylbenzene following intermediate-duration inhalation exposure. The available animal studies suggest that ototoxicity is the most sensitive end point of ethylbenzene toxicity. Rats exposed to ≥400 ppm ethylbenzene via inhalation for 4 or 13 weeks showed significant increases in auditory thresholds. These threshold shifts persisted unchanged for the duration of the exposure period and during an 8-week post-exposure recovery period (Gagnaire et al. 2007). Cell counts conducted in the organ of Corti after the 8-week recovery period showed significant losses of outer hair cells in rats exposed to ≥200 ppm. Concentration-related losses of inner hair cells (IHC) (14 and 32%) were observed in animals in the 600 and 800 ppm groups, respectively, with occasional IHC losses in the 400 ppm group.

Systemic effects have been observed at concentrations equal to or higher than those that elicited ototoxic effects in rats. Increased liver, kidney, lung, and spleen weights have been observed in animals exposed to ethylbenzene concentrations in the 250–1,000 ppm range (Cragg et al. 1989; Elovaara et al. 1985; NIOSH 1981; NTP 1992; Wolf et al. 1956). However, the changes in organ weight have not been associated with histological alterations. One study (Cragg et al. 1989) reported a small, but statistically significant, increase in platelet counts in male rats and leukocyte counts in female rats exposed to 782 ppm ethylbenzene for 4 weeks. Developmental effects have been observed in rats exposed to ≥1,000 ppm. Increases in the occurrence of skeletal malformations (NIOSH 1981; Saillenfait et al. 2003) and decreases in fetal body weight (Saillenfait et al. 2003, 2006, 2007) have been observed at ≥1,000 ppm. The NOAEL for these effects is 500 ppm (NIOSH 1981; Saillenfait et al. 2003, 2006, 2007). Developmental landmarks and neurodevelopment were not statistically or biologically

significantly affected in the offspring of rats exposed to up to 500 ppm ethylbenzene in a two-generation reproductive toxicity study (Faber et al. 2006, 2007).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, Heraline Hicks

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 62
Species: Rat

Minimal Risk Level: 0.06 [ ] mg/kg/day [x] ppm

Reference: NTP. 1999. NTP technical report on the toxicology and carcinogenesis studies of ethylbenzene in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. NTP TR 466.

Experimental design: Groups of F344/N rats (50 animals/sex/dose group) were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation for 6 hours/day, 5 days/week for 104 weeks. Animals were observed twice daily and clinical findings were recorded monthly. Body weights were recorded at the initiation of the study, weekly for the first 13 weeks, at week 16, monthly through the end of exposure, and prior to terminal necropsy. Animals that survived to study termination were killed by asphyxiation with CO_2. A complete necropsy and microscopic examination were performed on all rats and mice that survived to study termination or died early. The tissues examined included the adrenal gland, blood vessel (aorta), bone and marrow, brain, clitoral gland, esophagus, gall bladder, harderian gland, heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

Effect noted in study and corresponding doses: Survival of male rats in the 750-ppm group was significantly less than that of control animals. Survival was not affected in rats in other exposure groups or in mice at any ethylbenzene concentration. No clinical findings were attributed to ethylbenzene exposure in rats or mice. Although the incidence of nephropathy (47/50, 43/50, 47/50, and 48/50 in males and 38/50, 42/50, 43/50, and 46/49 in females) was not significantly different between the groups, significant increases in the severity of the nephropathy were observed in females at ≥75 ppm and in males at 750 ppm. The nephropathy severity scores in the 0, 75, 250, and 750 ppm groups were 2.3, 2.4, 2.3, and 3.5 in males, respectively, and 1.3, 1.6, 1.7, and 2.3 in females, respectively. Additionally, significant increases in the incidences of renal tubule hyperplasia were observed in male rats exposed to 750 ppm. The incidences of renal tubule adenoma and adenoma or carcinoma (combined) in the 750 ppm group were significantly greater than the incidence in control animals. An increase in the incidence of cystic degeneration of the liver was also observed in male rats at 750 ppm.

Dose and end point used for MRL derivation: The critical effect for chronic exposure to ethylbenzene is increased severity of chronic progressive nephropathy in female rats exposed to 75 ppm and higher (NTP 1999). BMD analysis was considered for determining the point of departure for the MRL; however, none of the available continuous exposure BMD models fit the data (standard errors were calculated using the raw severity score data). Thus, a NOAEL/LOAEL approach was selected for calculating the point of departure.

[ ] NOAEL [x] LOAEL

Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure concentrations ranging from 1 to 50 ppm. Two internal dose metrics were simulated for kidney effects: time-averaged arterial blood concentration of ethylbenzene (MCA) and time-averaged rate of metabolism of ethylbenzene expressed per kg body mass (MRAMKB). Both metrics were explored because current knowledge of the mechanisms of toxicity of ethylbenzene does not include an understanding of the relative contribution of parent compound or metabolites as proximate toxic agents in kidney. The assumption in using the MCA metric for this end point is that tissue dosimetry and response would be correlated with time-averaged arterial ethylbenzene concentration (or average x time, AUC), which would be expected to correlate with time-averaged kidney concentration. The assumption in using the MRAMKB metric is that the kidney response is correlated with the time-averaged rate of whole-body production of ethylbenzene metabolites. In the model, all metabolism is attributed to the liver (the model does not have a kidney compartment); therefore, the rate of metabolism in the liver is the only representation of whole body metabolism that can be simulated. The internal dose metrics (MCA and MRAMKB) for each exposure level are presented in Table A-9.

Table A-9. Internal Dose Metrics for Male and Female F344/N Rats Exposed to Ethylbenzene 6 Hours/Day, 5 Days/Week for 104 Weeks

Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	MRAMKB (µmol/hour/kg body weight)
Male[a]		
0	0	0
75	4.12	8.92
250	27.66	23.64
750	146.77	43.05
Female[b]		
0	0	0
75	4.16	10.00
250	28.72	26.04
750	150.68	46.49

[a]Time weighted average body weight of 0.43 kg.
[b]Time weighted average body weight of 0.27 kg.

MCA = time-averaged arterial blood concentration; MRAMKB = time averaged rate of ethylbenzene metabolism expressed per kg body mass

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: The human PBPK model was used to predict HECs corresponding to $LOAEL_{MCA}$ and $LOAEL_{MRAMKB}$ in female rats. The MCA and MRAMKB dose metrics were converted to HEC values by iterative simulation of human inhalation exposures. Exposure concentrations were varied until the simulated value for the internal dose metric was within 0.01% of the LOAEL. The HECs were 17.45 ppm for the MCA dose metric and 52.68 ppm for the MRAMKB dose metric. Because there is limited information to determine whether the observed renal toxicity in female rats exposed to ethylbenzene is due to ethylbenzene or its metabolites, the lowest HEC value (17.45 ppm) was selected as the point of departure for the MRL.

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HECs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: The chronic toxicity of inhaled ethylbenzene has been examined humans and in 2-year bioassays in rats and mice conducted by NTP (1999). Hematological effects (increased average number of lymphocytes and decreased hemoglobin) were observed in workers exposed to solvents containing ethylbenzene (Angerer and Wulf 1985). In rats, concentration-related increases in the severity of nephropathy were observed in female rats exposed to ≥75 ppm and in male rats exposed to 750 ppm (NTP 1999). Increases in the incidence of renal tubule hyperplasia were also observed in male and female rats exposed to 750 ppm. The lowest LOAEL identified in mice was 250 ppm for hyperplasia of pituitary gland pars distalis observed in females; at 750 ppm, thyroid follicular cell hyperplasia was observed in male and female mice and hypertrophy and necrosis of the liver were observed in male mice.

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, Heraline Hicks

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 0.4 [x] mg/kg/day [ ] ppm

Reference: Mellert W, Deckardt K, Kauffmann W, et al. 2007. Ethylbenzene: 4- and 13-week rat oral toxicity. Arch Toxicol 81:361-370.

Experimental design: Groups of 10 male and 10 female Wister rats were administered ethylbenzene (no vehicle) by oral gavage at doses of 0, 75, 250, or 750 mg/kg/day for 13 weeks. The total daily dose of ethylbenzene was administered as split morning/evening half doses. Animals were examined daily for mortality and clinical signs. Food and water consumption and body weights were recorded weekly. A detailed clinical examination [ophthalmology and a functional observational battery (FOB)] and assessment of motor activity were conducted during the last week of treatment. After 13 weeks, urinalysis was conducted and blood samples were obtained and analyzed for hematology and clinical chemistry; organ weights were recorded and gross histopathologic examinations of the liver, kidney, and pancreas were conducted on animals in all groups. A comprehensive histopathological examination of tissues was performed in the control and 750 mg/kg/day groups.

Effect noted in study and corresponding doses: Clinical signs (post-dosing salivation) in treated animals were observed in all animals administered ≥250 mg/kg/day and in one animal administered 75 mg/kg/day. Terminal body weight in males was significantly decreased by 14% compared to controls in the 750 mg/kg/day group. Mean corpuscular volume was increased in males and females and platelet count was reduced in females treated with 750 mg/kg/day. Effects indicative of liver toxicity included increased activity of serum liver enzymes (alanine aminotransferase and γ-glutamyl transferase) in males (≥250 mg/kg/day) and females (750 mg/mg/day), increased absolute and relative liver weights (≥250 mg/kg/day in males and females), and a dose-related increase in the incidence of centrilobular hepatocyte hypertrophy (≥250 mg/kg/day in males and females) (Table A-10). Increased bilirubin (≤250 mg/kg/day in males and 750 mg/kg/day in females), total protein (750 mg/kg/day in females), albumin (750 mg/kg/day in males and females), globulins (750 mg/kg/day in females), and cholesterol (≤250 mg/kg/day in males and females), and decreased prothrombin time (750 mg/kg/day in males and ≥250 mg/kg/day in females) were considered by study investigators as adaptive effects in the liver. In males in the 75 mg/k/day group, relative liver weight was significantly increased by (4% compared to controls); however, no histopathological changes or increases in absolute liver or serum liver enzyme activities were observed at this dosage. Given that ethylbenzene is a microsomal enzyme inducer and the absence of histopathology and other evidence of liver injury at the 75 mg/kg/day dosage, the small increase in relative liver weight in male rats at this dosage was not considered indicative of an adverse effect on the liver.

Table A-10. Effects on Serum Liver Enzymes, Liver Weights, and Liver Histopathology in Male and Female Rats Exposed to Oral Ethylbenzene for 13 Weeks

Parameter	Dose group (mg/kg/day)			
	0	75	250	750
		Males		
ALT (µkat/L)	0.62±0.12[a]	0.70±0.12	0.89±0.26[b]	1.11±0.23[b]
GGT (nkat/L)	2±3	6±6	10±6[b]	10±6[b]
Absolute liver weight (g)	8.02±0.55	8.26±0.81	10.25±0.98[b]	9.88±0.98[b]
Liver/body weight (%)	2.26±0.08	2.36±0.08[b]	3.01±0.14[b]	3.31±0.13[b]
Centrilobular hepatocyte hypertrophy (incidence)	1/10	1/10	6/10[c]	8/10[b]
		Females		
ALT(µkat/L)	0.58±0.18	0.55±0.08	0.60±0.12	0.73±0.19[c]
Absolute liver weight (g)	5.40±0.30	5.72±0.53	6.11±0.36[b]	7.15±0.50[b]
Liver/body weight (%)	2.63±0.13	2.70±0.16	3.03±0.12[b]	3.52±0.18[b]
Centrilobular hepatocyte hypertrophy (incidence)	0/10	0/10	5/10[c]	10/10[b]

[a]values are mean±standard deviation.
[b]p≤0.01.
[c]p≤0.05.

ALT = alanine aminotransferase; GGT = γ-glutamyl transferase

Source: Mellert et al. 2007

Renal effects in males included increased serum creatinine (750 mg/kg/day), increased incidences of transitional epithelial cells and granular and epithelial cell casts in the urine (≥250 mg/kg/day), increased absolute and relative kidney weights (≥250 mg/kg/day), and a dose-related increase in severity of hyaline droplet nephropathy (≥250 mg/kg/day). Adverse renal effects in males were most likely related to accumulation of α2µ-globulin, and, therefore, considered not relevant to humans. Absolute kidney weight was significantly increased by 7 and 13% in females administered 250 and 750 mg/kg/day, respectively, compared to controls; however, since no histopathological findings or alterations in urinalysis parameters were observed, the increased kidney weight in females was not considered indicative of an adverse kidney effect in female rats. Absolute and relative thymus weights were decreased in females treated with ≥250 mg/kg/day, but no histopathological findings were observed. Results of the FOB did not reveal consistent treatment-related effects.

Dose and end point used for MRL derivation: Based on evidence of hepatotoxicity (increased serum liver enzyme activity, absolute and relative liver weights, and incidence of centrilobular hepatocyte hypertrophy), the liver was identified as the most sensitive target for oral ethylbenzene, with NOAEL and LOAEL values of 75 and 250 mg/kg/day, respectively. Since serum liver enzyme activities were increased in the 250 and 750 mg/kg/day groups in males, but only in the 750 mg/kg/day group in females, males appeared more sensitive than females to hepatic effects of oral ethylbenzene. BMD analysis was used to identify points of departure for several liver endpoints (alanine aminotransferase activity,

γ-glutamyl transferase activity, absolute liver weight, relative liver weight, and centrolobular hepatocyte hypertrophy) using the two internal dose metrics.

[ ] NOAEL [ ] LOAEL [X] BMDL

To determine the point of departure for derivation of the intermediate-duration MRL, a PBPK model was used to estimate internal dose metrics and data sets for serum liver enzymes, absolute and relative liver weight, and centrilobular hepatocyte hypertrophy (Table A-10) in male rats were evaluated for suitability for BMD modeling. Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure concentrations ranging from 1 to 50 ppm. The model was extended to implement first-order gastrointestinal absorption kinetics as described in Faber et al. (2006). For liver effects, the model simulated two internal dose metrics: time-averaged concentration of ethylbenzene in liver (MCL) and time-averaged rate of metabolism of ethylbenzene in liver (MRAMKL). The assumption of using the MCL metric is that the liver response is correlated with the time-averaged concentration of ethylbenzene in liver. The assumption in using the MRAMKL metric is that the liver response is correlated with the time-averaged rate of production of ethylbenzene metabolites in liver. Both metrics were explored because current knowledge of the mechanism of toxicity of ethylbenzene does not include an understanding of the relative contributions of parent compound or metabolites as proximate toxic agents in liver.

Data for changes in alanine aminotransferase and γ-glutamyl transferase, absolute liver weight and relative liver weight were analyzed using all available continuous variable models in EPA BMDS (version 2.1.1). BMDs and the 95% lower confidence limit on the BMD (BMDLs) associated with a BMR of 1 standard deviation change from the control were calculated for all models. The data were fit to BMD models using the MCL and MRAMKL internal dose metrics. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power and Hill models are fit to the data and evaluated while the variance model is applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling.

As summarized in Table A-11, the alanine aminotransferase activity data only adequately fit the Hill model (Figure A-9) and absolute liver weight data only fit the linear model with nonconstant variance (Figure A-10) when MCL was used as the internal dose metric. Three models fit the data (using MCL as the internal dose metric) for relative liver weight when the highest dose was dropped (linear, 2-degree polynomial, and power models); the linear model is presented in Figure A-11. No models meet adequate fit criteria for γ-glutamyl transferase when MCL was used as the internal dose metric.

Table A-11. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, and Absolute and Relative Liver Weight Using Liver Ethylbenzene Concentration (MCL) Dose Metric in Male Rats Exposed to Ethylbenzene Via Gavage for 13 Weeks Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/L)	$BMDL_{1SD}$ (μmol/L)
Alanine aminotransferase					
All doses					
Constant variance					
Linear[b]	0.02	0.04	-83.16	NA	NA
Nonconstant variance					
Hill[c]	**0.34**	**0.83**	**-93.15**	**21.34**	**7.49**
Linear[b]	0.34	0.001	-82.16	NA	NA
Polynomial (2-degree)[b]	0.34	0.001	-82.16	NA	NA
Polynomial (3-degree)[b]	0.34	0.001	-82.16	NA	NA
Power[c]	0.34	0.001	-82.16	NA	NA
γ-Glutamyl transferase	Inadequate fit to all models				
Absolute liver weight					
All doses					
Constant variance					
Hill[c]	0.28	NA	33.68	NA	NA
Linear[b]	0.28	<0.0001	56.22	NA	NA
Polynomial (2-degree)[b]	0.28	<0.0001	56.22	NA	NA
Polynomial (3-degree)[b]	0.28	<0.0001	56.22	NA	NA
Power[c]	0.28	<0.0001	56.22	NA	NA
Highest dose dropped					
Constant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	**0.20**	**0.87**	**19.46**	**42.31**	**32.17**
Polynomial (2-degree)[b]	0.20	0.87	19.46	42.31	32.17
Power[c]	0.20	0.87	19.46	42.31	32.17
Relative liver weight					
All doses					
Constant variance					

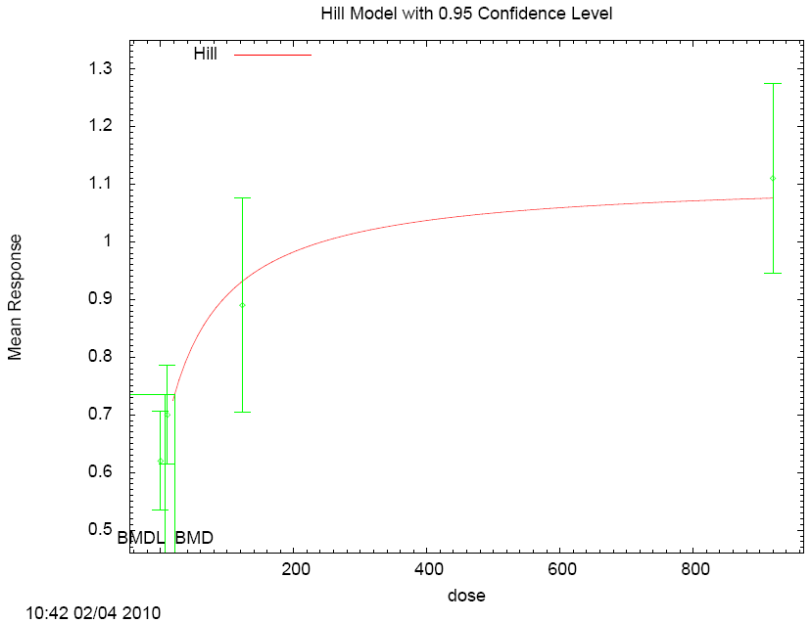
Table A-11. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, and Absolute and Relative Liver Weight Using Liver Ethylbenzene Concentration (MCL) Dose Metric in Male Rats Exposed to Ethylbenzene Via Gavage for 13 Weeks Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/L)	$BMDL_{1SD}$ (μmol/L)
Hill[c]	0.15	NA	-130.06	NA	NA
Linear[b]	0.15	<0.0001	-60.07	NA	NA
Polynomial (2-degree)[b]	0.15	<0.0001	-60.07	NA	NA
Polynomial (3-degree)[b]	0.15	<0.0001	-60.07	NA	NA
Power[c]	0.15	<0.0001	-60.07	NA	NA
Highest dose dropped					
Constant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	**0.11**	**0.39**	**-102.26**	**16.74**	**13.53**
Polynomial (2-degree)[b]	0.11	0.39	-102.26	16.74	13.53
Power[c]	0.11	0.39	-102.26	16.74	13.53

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

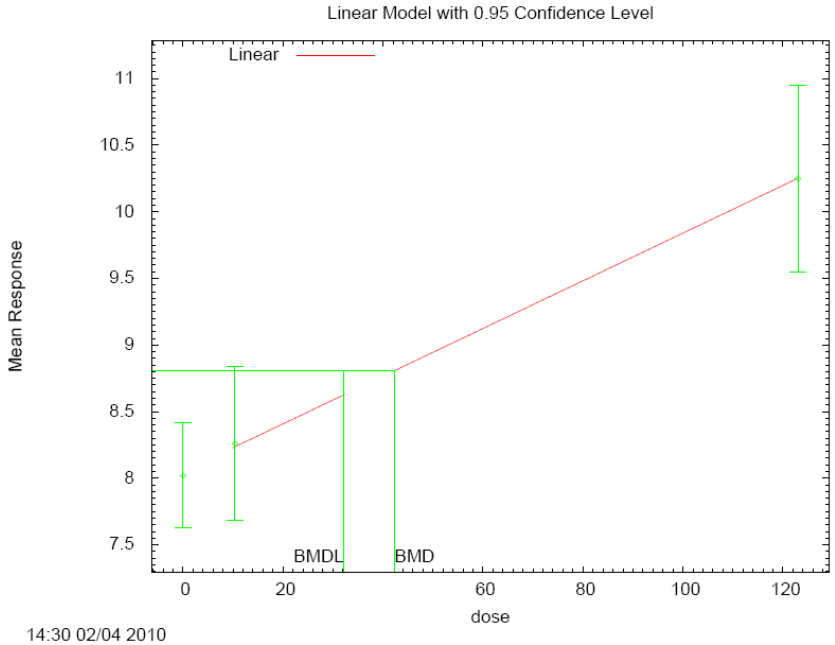
AIC = Akaike Information Criterion; BMD_{1SD} = benchmark dose associated with the benchmark response of 1 standard deviation (SD); BMDL = 95% lower confidence limit on the BMD; MCL = time-averaged concentration of ethylbenzene in liver; NA = not applicable, model does not provide adequate fit to the data

Figure A-9. Predicted (Hill Model with Nonconstant Variance) and Observed Changes in Alanine Aminotransferase Levels Using MCL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

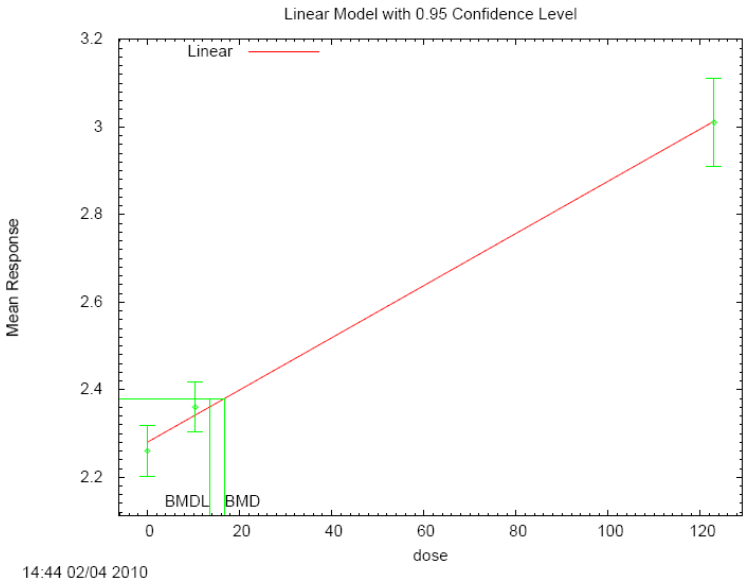
Figure A-10. Predicted (Linear Model with Constant Variance) and Observed Changes in Absolute Liver Weight Using MCL Internal Dose Metric*



Highest dose dropped

*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

Figure A-11. Predicted (Linear Model with Constant Variance) and Observed Changes in Relative Liver Weight Using MCL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

The model predictions using the MRAMKL internal dose metric are summarized in Table A-12. Several models fit the alanine aminotransferase data, the 3-degree polynomial model with nonconstant variance had the lowest AIC and is illustrated in Figure A-12. The linear, 2-degree polynomial, 3-degree polynomial, and power models all meet adequate fit criteria to the γ-glutamyl transferase data; Figure A-13 shows the fit of the linear model. The Hill model (Figure A-14) was the only model which provided adequate fit to the absolute liver weight data. Several models fit the relative liver weight data, the 2-degree polynomial model provided the best fit, as judged by the AIC; this model is shown in Figure A-15.

Table A-12. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, Absolute Liver Weight, and Relative Liver Weight in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/hour/kg liver)	$BMDL_{1SD}$ (μmol/hour/kg liver)
Alanine aminotransferase					
All doses					
Constant variance					
Linear[b]	0.02	0.14	-85.87	NA	NA
Nonconstant variance					

Table A-12. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, Absolute Liver Weight, and Relative Liver Weight in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/hour/kg liver)	$BMDL_{1SD}$ (μmol/hour/kg liver)
Hill[c]	0.34	NA	-90.93	NA	NA
Linear[b]	0.34	0.26	-92.47	438.99	307.25
Polynomial (2-degree)[b]	0.34	0.65	-92.98	771.05	387.82
Polynomial (3-degree)[b]	**0.34**	**0.81**	**-93.14**	**804.09**	**391.02**
Power[c]	0.34	0.61	-92.93	778.16	388.97
γ-Glutamyl transferase					
All doses					
Constant variance					
Hill[c]	0.14	NA	180.82	NA	NA
Linear[b]	**0.14**	**0.73**	**177.46**	**1,072.23**	**737.62**
Polynomial (2-degree)[b]	0.14	0.73	177.46	1,072.23	737.62
Polynomial (3-degree)[b]	0.14	0.73	177.46	1,072.23	737.62
Power[c]	0.14	0.73	177.46	1,072.23	737.62
Absolute liver weight					
All doses					
Constant variance					
Hill[c]	**0.28**	**0.31**	**31.68**	**602.99**	**548.01**
Linear[b]	0.28	0.05	34.73	NA	NA
Polynomial (2-degree)[b]	0.28	0.01	36.61	NA	NA
Polynomial (3-degree)[b]	0.28	0.01	36.61	NA	NA
Power[c]	0.28	0.02	36.29	NA	NA
Relative liver weight					
All doses					
Constant variance					
Hill[c]	0.15	NA	-130.06	NA	NA
Linear[b]	0.15	<0.0001	-107.43	NA	NA
Polynomial (2-degree)[b]	**0.15**	**0.96**	**-133.98**	**531.76**	**390.47**

Table A-12. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, Absolute Liver Weight, and Relative Liver Weight in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

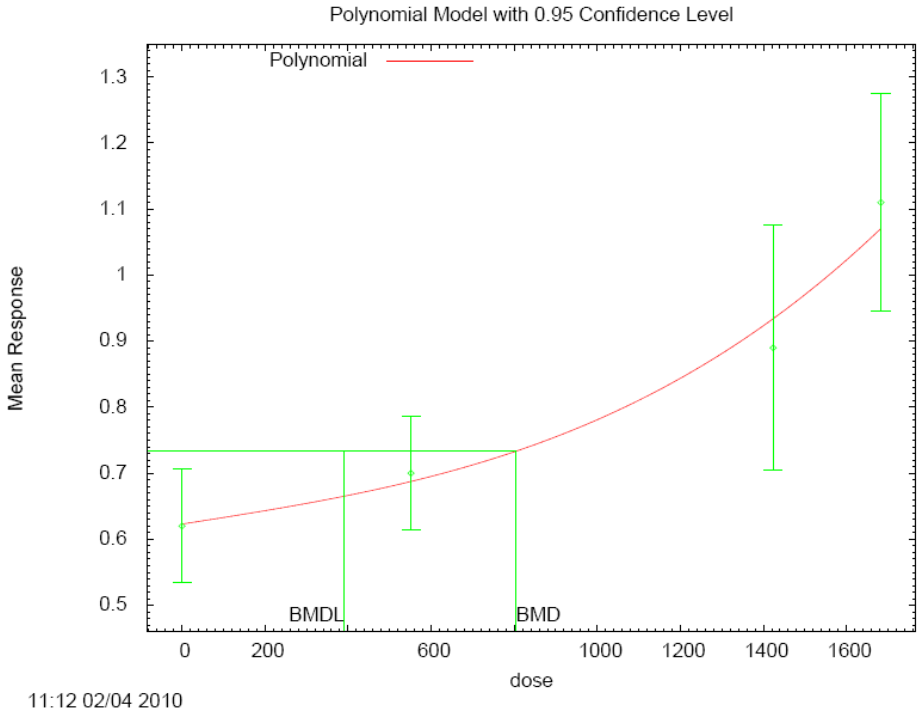
Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/hour/kg liver)	$BMDL_{1SD}$ (μmol/hour/kg liver)
Polynomial (3-degree)[b]	0.15	0.80	-132.00	540.34	485.79
Power[c]	0.15	0.83	-132.02	547.45	416.38

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response of 1 standard deviation (SD); BMDL = 95% lower confidence limit on the BMD; MRAMKL = time-averaged rate of metabolism of ethylbenzene in liver; NA = not applicable, model does not provide adequate fit to the data.

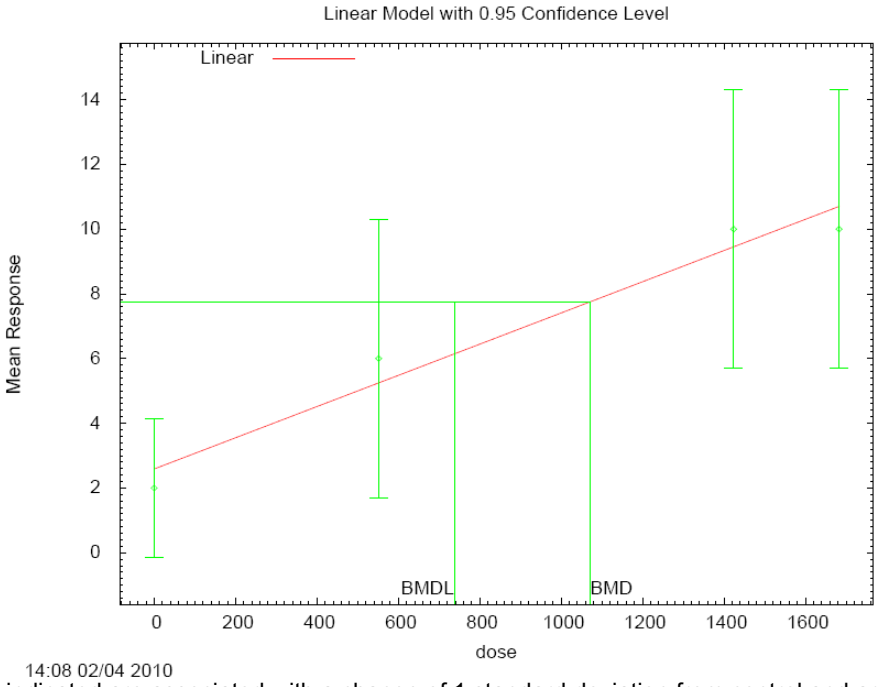
Source: Mellert et al. 2007

Figure A-12. Predicted (3-Degree Polynomial with Nonconstant Variance) and Observed Changes in Alanine Aminotransferase Using MRAMKL Internal Dose Metric*



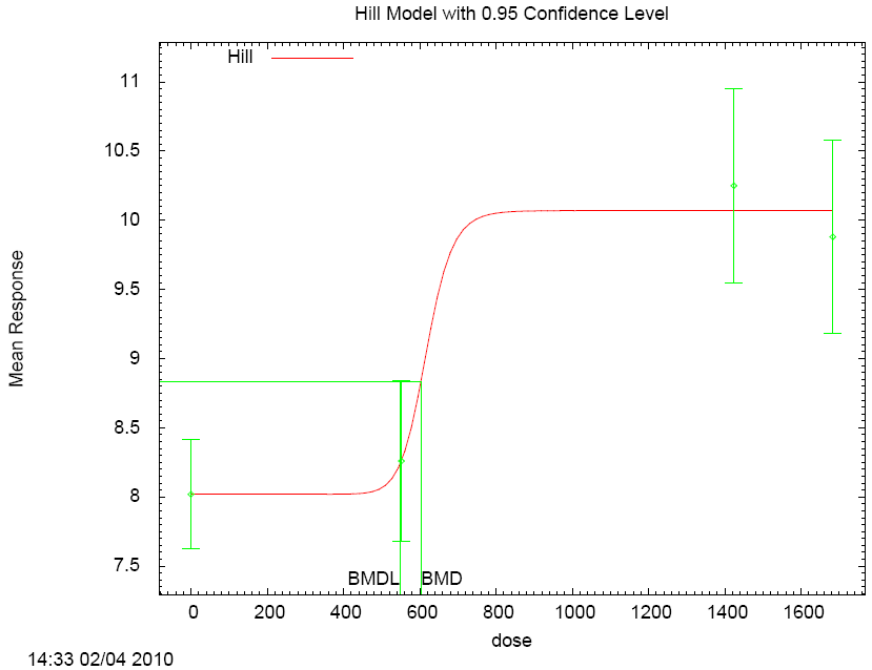
*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of μmol/hour/kg liver.

Figure A-13. Predicted (Linear Model with Nonconstant Variance) and Observed Changes in γ-Glutamyl Transferase Using MRAMKL Internal Dose Metric*



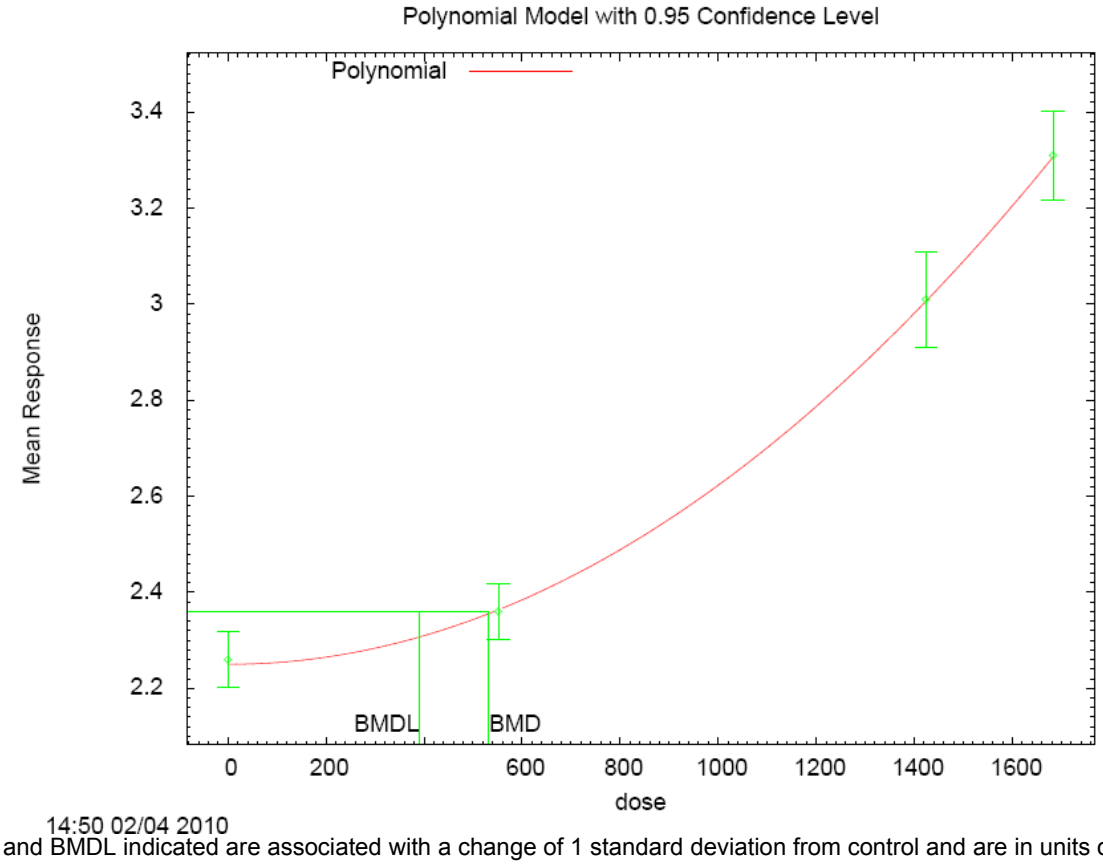
*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of μmol/hour/kg liver.

Figure A-14. Predicted (Hill Model with Constant Variance) and Observed Changes in Absolute Liver Weight Using MRAMKL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of μmol/hour/kg liver.

Figure A-15. Predicted (2-Degree Polynomial Model with Constant Variance) and Observed Changes in Relative Liver Weight Using MRAMKL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of µmol/hour/kg liver.

Data for the incidence of centrilobular hepatocyte hypertrophy were analyzed using all available dichotomous models in the EPA BMDS (version 2.1.1) using the extra risk option. The multistage model was run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models meeting adequate fit criteria, the lowest BMDL was selected as the point of departure when the difference between the BMDLs estimated from these models were more than 3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. BMDs and lower bounds on the BMD (BMDLs) associated with a BMR of 10% extra risk were calculated for all models. The data were fit to BMD models using the MCL and MRAMKL dose metrics. The BMD models using the MCL dose metric are summarized in Table A-13. As assessed by the chi-square goodness-of-fit statistic, most of the models using the MCL dose metric provided adequate fit to the data. The BMDs ranged from 16.51 to 127.56 µmol/L and the BMDLs ranged from 6.61 to 76.55 µmol/L. Because the range of BMDLs was greater than threefold; the lowest BMDL was selected as a point of departure. The log logistic model estimated the lowest BMDL of 6.61 µmol/L; the fit of this model is presented in Figure A-16.

Table A-13. Model Predictions for the Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MCL Internal Dose Metric

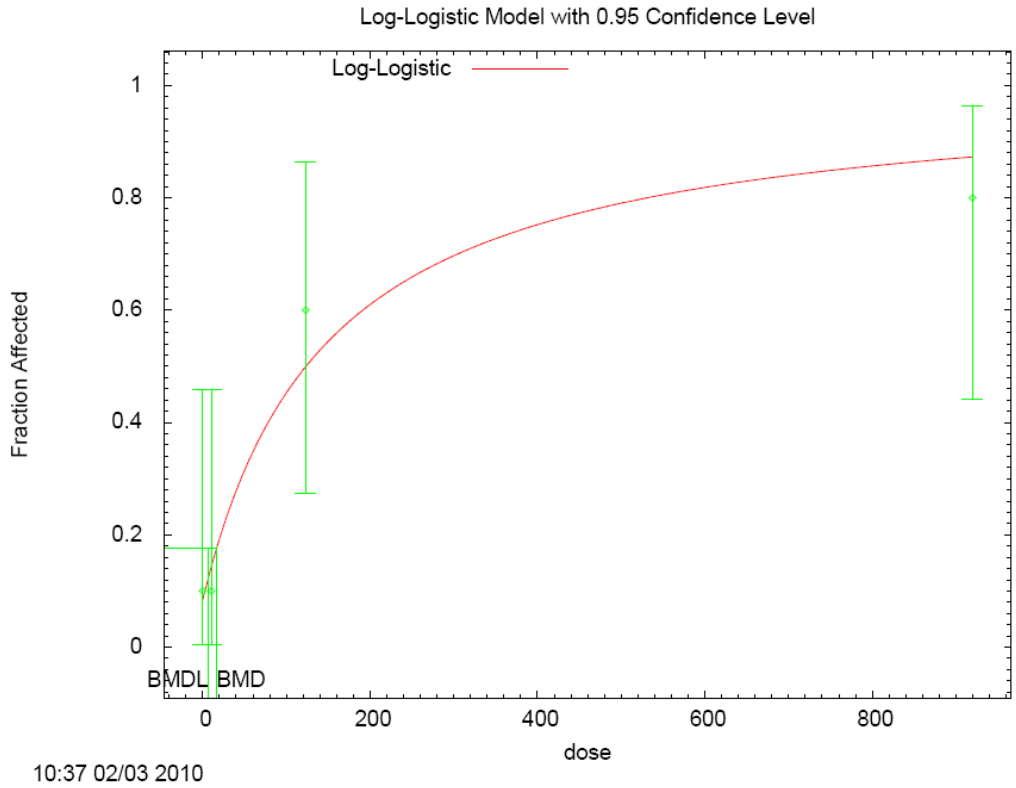
Model	χ^2 Goodness-of-fit p-value[a]	AIC	BMD_{10} (µmol/L)	$BMDL_{10}$ (µmol/L)
Gamma[b]	0.13	44.25	48.12	26.42
Logistic	0.04	46.66	127.56	76.55
Log Logistic	**0.59**	**41.50**	**16.51**	**6.61**
Log Probit	0.07	44.67	NA	NA
Multistage (1-degree polynomial)[c]	0.13	44.25	48.12	26.42
Multistage (2-degree polynomial)[c]	0.13	44.25	48.12	26.42
Multistage (3-degree polynomial)[c]	0.13	44.25	48.12	26.42
Probit	0.04	46.62	NA	NA
Weibull[b]	0.13	44.25	48.12	26.42
Quantal-Linear	0.13	44.25	48.12	26.42

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Betas restricted to ≥0.

AIC = Akaike Information Criteria; BMD = benchmark dose associated with the selected benchmark response of 10% extra risk; BMDL = 95% lower confidence limit on the BMD; NA = not applicable, the data did not adequately fit the model

Source: Mellert et al. 2007

Figure A-16. Predicted (Log Logistic Model) and Observed Incidence of Centrilobular Hepatocyte Hypertrophy*



*BMDs and BMDLs indicated are associated with 10% extra risk and are in units of µmol/L.

The BMD models using the MRAMKL dose metric are presented in Table A-14. All models provided adequate fit to the data (χ^2 p>0.1). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the multistage 3-degree polynomial model (Figure 17) provided the best fit to the data. The BMD_{10} and $BMDL_{10}$ predicted by this model for the data on centrilobular hepatocyte hypertrophy in male rats were 704.21 and 206.91 µmo/hour/kg liver, respectively.

Because there is limited information to determine whether the observed hepatic effects are due to ethylbenzene or its metabolites, the lowest BMDL value (6.61 µmol/L, MCL dose metric) was selected as the point of departure for the MRL.

Table A-14. Model Predictions for the Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Administered Ethylbenzene Via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

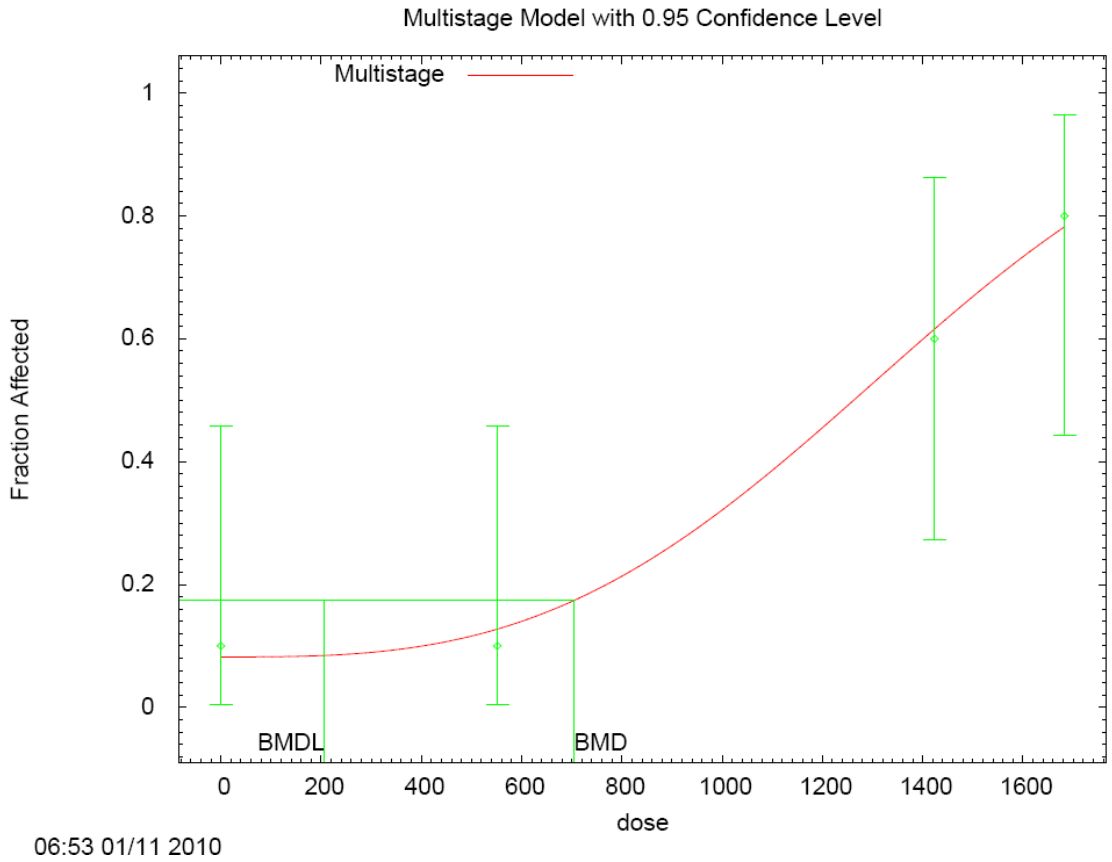
Model	χ^2 Goodness-of-fit p-value[a]	AIC	BMD_{10} (µmol/hour/kg liver)	$BMDL_{10}$ (µmol/hour/kg liver)
Gamma[b]	0.99	42.47	937.22	283.42
Logistic	0.62	41.38	480.93	300.24
Log Logistic	0.98	42.47	961.63	313.44
LogProbit	1.00	42.47	973.00	332.90
Multistage (1-degree polynomial)[c]	0.18	44.50	178.95	113.79
Multistage (2-degree polynomial)[c]	0.65	41.42	483.71	179.74
Multistage (3-degree polynomial)[c]	**0.93**	**40.61**	**704.21**	**206.91**
Probit	0.55	41.64	426.74	278.66
Weibull[b]	0.88	42.49	849.57	267.67
Quantal-Linear	0.18	44.50	178.95	113.79

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]Power restricted to ≥1
[c]Betas restricted to ≥0

AIC = Akaike Information Criteria; BMD = benchmark dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD

Source: Mellert et al. 2007

Figure A-17. Predicted (Multistage, 3-Degree Polynomial Model) and Observed Incidence of Centrilobular Hepatocyte Hypertrophy*



*BMDs and BMDLs indicated are associated with 10% extra risk and are in units of µmol/hour/kg liver.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a less serious LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustments
[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: For each end point and dose metric, human equivalent doses (HEDs) were predicted for the BMDL value with the lowest AIC (if multiple BMD models met the adequate fit criteria) using the human PBPK model. The BMDL values for the internal dose metrics (MCL and MRAMKL) were converted to HED values by iterative simulation of human oral exposures. Exposure doses (mg/kg/day) were varied until the simulated value for the internal dose metric was within 0.01% of the BMDL. The HEDs are summarized in Tables A-15 and A-16.

Table A-15. Human Equivalent Doses for Liver Effects Using MCL Internal Dose Metric

Effect	Model	BMDL (µmol/L)	HED[a] (mg/kg/day)
Increased alanine aminotransferase	Hill (all doses); constant variance	7.49	11.82
Increased γ-glutamyl transferase	Inadequate fit to all models		
Increased absolute liver weights	Linear (highest dose dropped); constant variance	32.17	31.82
Increased relative liver weights	Linear (highest dose dropped); constant variance	13.53	18.47
Centrilobular hepatocyte hypertrophy	Log logistic	6.61	10.68

[a]Calculated using a reference human body weight of 70 kg and the assumption that the daily dose was delivered in 16 dose splits/24 hours (i.e., only exposed during waking hours).

BMDL = 95% lower confidence limit on the benchmark dose; HED = human equivalent dose; MCL = time-averaged concentration of ethylbenzene in liver

Table A-16. Human Equivalent Doses for Liver Effects Using MRAMKL Internal Dose Metric

Effect	Model[a]	BMDL (µmol/hour/kg liver)	HED[b] (mg/kg/day)
Increased alanine aminotransferase	3-Degree polynomial; nonconstant variance	391.02	31.06
Increased γ-glutamyl transferase	Linear; constant variance	737.62	111.37[c]
Increased absolute liver weights	Hill; constant variance	548.01	48.62
Increased relative liver weights	2-Degree polynomial; constant variance	390.47	31.01
Centrilobular hepatocyte hypertrophy	Multistage (3-degree polynomial)	206.91	15.48

[a]All doses used for BMD modeling.
[b]Calculated using a reference human body weight of 70 kg and the assumption that the daily dose was delivered in 16 dose splits/24 hours (i.e., only exposed during waking hours).
[c]Approximate value, value is very close to the metabolism Vmax.

BMDL = 95% lower confidence limit on the benchmark dose; MRAMKL = time-averaged rate of metabolism of ethylbenzene in liver

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HEDs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: The intermediate-duration oral database for ethylbenzene is limited to a study conducted by Mellert et al. (2007) evaluating the effects of oral exposure of rats to ethylbenzene for 4 and 13 weeks, and a poorly reported 6-month

exposure study in rats (Wolf et al. 1956). The 4- and 13-week studies by Mellert et al. (2007) found effects consistent with hepatotoxicity including increased absolute and relative liver weights, increased incidence of hepatocyte centrilobular hypertrophy, and increased serum liver enzyme activities in rats administered ≥250 mg/kg/day. Kidney effects, including increases in increases in relative kidney weight and hyaline droplet nephropathy were observed in males administered ≥250 mg/kg/day; however, these effects were most likely secondary to increases accumulation of accumulation of α2μ-globulin accumulation, and, therefore, considered not relevant to humans. Wolf et al. (1956) also reported liver effects (characterized by cloudy swelling of parenchymal cells of the liver and an increase in liver weight were observed in female rats administered 408 mg/kg/day by gavage for 6 months (Wolf et al. 1956). No other hepatic changes were reported. However, this study was poorly reported and did not provide adequate descriptions of study methods or results.

Although no additional data are available regarding the effects of intermediate oral exposure to ethylbenzene, results of an acute-duration oral study indicate that ethylbenzene is ototoxic (Gagnaire and Langlais 2005). In male rats administered 900 mg/kg/day (the only dose tested) by gavage for 2 weeks, an almost complete loss of the three rows of OHCs in the organ of Corti was observed in male rats (Gagnaire and Langlais 2005). The 4- and 13-week oral studies by Mellert et al. (2007) did not examine the cochlea or measure auditory function.

Acute (Cappaert et al. 1999, 2000, 2001, 2002) and intermediate (Gagnaire et al. 2007) inhalation studies and an acute oral study (Gagnaire and Langlais 2005) have identified ototoxicity as a sensitive effect of ethylbenzene exposure. Although intermediate-duration oral studies have not examined this potential endpoint, a comparison of the human equivalent dose for liver effects following oral exposure and the human equivalent concentration for ototoxicity following inhalation exposure can be made using the PBPK model developed for MRL derivation. The human PBPK model predicts that the HED (10.68 mg/kg/day) would result in an internal dose of 1.92 μmol/L for MCA (the relevant internal dose metric for ototoxicicty). The HEC that corresponds to an MCA of 1.92 μmol/L is 8.37 ppm. Therefore, the HED of 10.68 mg/kg/day would be equivalent to human equivalent air concentration of 8.37 ppm. This air concentration is about 8-fold lower than the HEC of 63.64 ppm used to derive the intermediate-duration inhalation MRL, suggesting that the liver is a more sensitive target of oral toxicity than the cochlea.

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, Heraline Hicks

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

SAMPLE

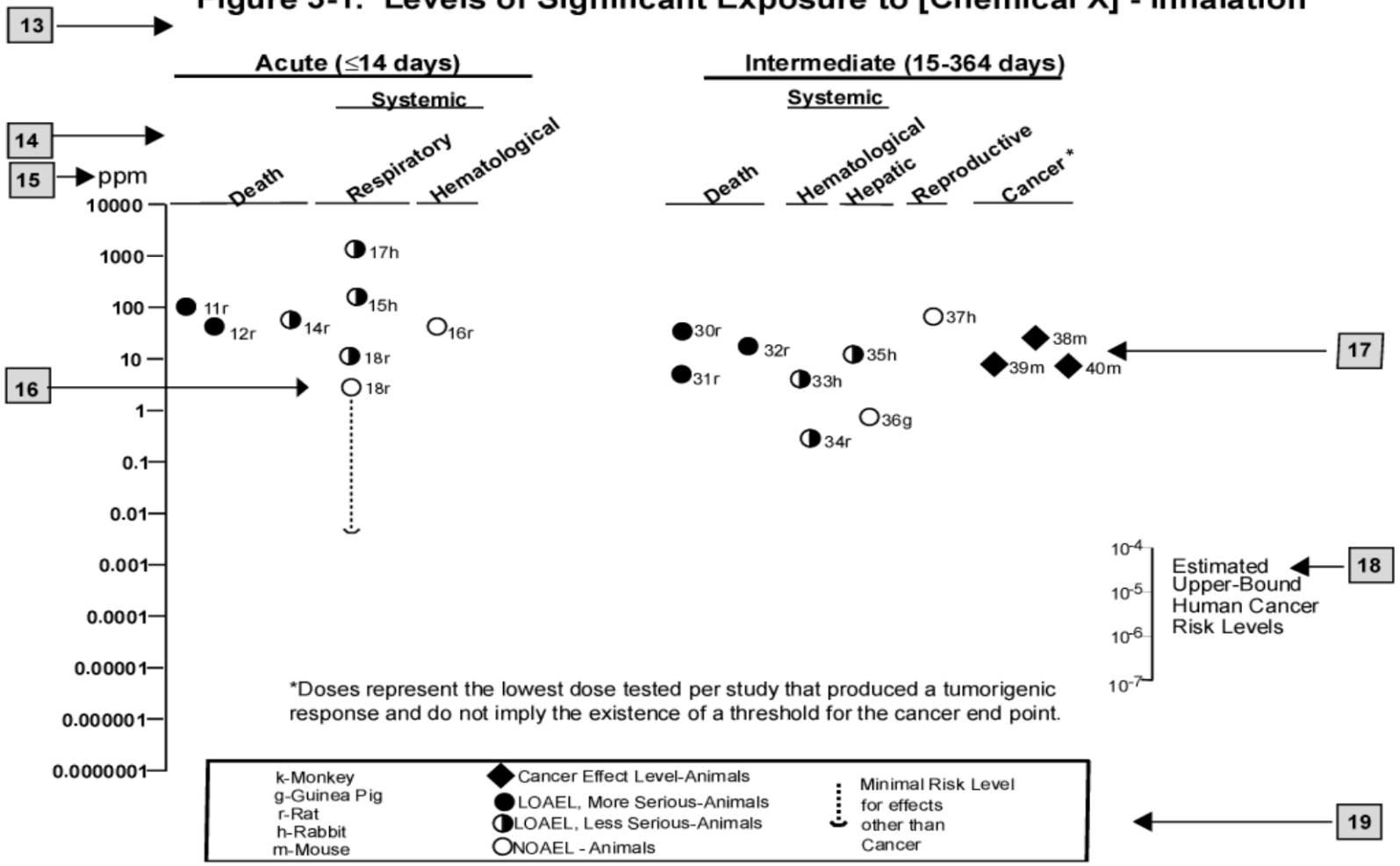
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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