TOXICOLOGICAL PROFILE FOR TOLUENE

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

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UPDATE STATEMENT

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

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FOREWORD

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

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

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

Each profile includes the following:

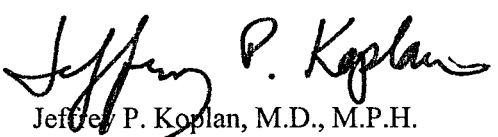
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

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

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



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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 21, 1999 (64 FR 56792). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988(53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); and November 17, 1997 (62 FR 61332). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

Section 1.6 How Can Toluene Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to Toluene?
Section 2.7 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.8 Biomarkers of Exposure and Effect
Section 2.11 Methods for Reducing Toxic Effects

ATSDR Information Center

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E-mail: atsdric@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@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1. Dr. Clint Skinner, Skinner Associates, 3985 Shooting Star Road, Creston, CA 93432; and

2. Dr. Robert G. Tardiff, 1423 Trapline Court, Vienna, VA 22189.

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

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

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1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Toluene has been found in at least 959 of the 1,591 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which toluene is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

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

1.1 WHAT IS TOLUENE?

Toluene is a clear, colorless liquid with a distinctive smell. It is a good solvent (a substance that can dissolve other substances). It is added to gasoline along with benzene and xylene. Toluene occurs naturally in crude oil and in the tolu tree. It is produced in the process of making gasoline and other fuels from crude oil, in making coke from coal, and as a by-product in the manufacture of styrene. Toluene is used in making paints, paint thinners, fingernail polish, lacquers, adhesives, and rubber and in some printing and leather tanning processes. It is disposed of at hazardous waste sites as used solvent or at landfills where it is present in discarded paints, paint

thinners, and fingernail polish. You can begin to smell toluene in the air at a concentration of 8 parts of toluene per million parts of air (ppm), and taste it in your water at a concentration of between 0.04 and 1 ppm. More information on the properties, production, and uses of toluene can be found in Chapters 3 and 4.

1.2 WHAT HAPPENS TO TOLUENE WHEN IT ENTERS THE ENVIRONMENT?

Toluene enters the environment when you use materials that contain it, such as paints, paint thinners, adhesives, fingernail polish, and gasoline. As you work with these materials, the toluene evaporates and becomes mixed with the air you breathe. Toluene enters surface water and groundwater (wells) from spills of solvents and petroleum products as well as from leaking underground storage tanks at gasoline stations and other facilities. Leaking underground storage tanks also contaminate the soil with toluene and other petroleum-product components.

When toluene-containing products are placed in landfills or waste disposal sites, the toluene can enter the soil and water near the waste site. Toluene does not usually stay in the environment; it is readily broken down to other chemicals by microorganisms in soil and evaporates from surface water and surface soils. Toluene dissolved in well water does not break down quickly while the water is under the ground because there are few microorganisms in underground water. Once the water is brought to the surface, the toluene will evaporate into the air.

Toluene can be taken up into fish and shellfish, plants, and animals living in water containing toluene, but it does not concentrate or build up to high levels because most animal species can break down the toluene into other compounds that are excreted.

More information on how toluene enters the environment and what happens to it can be found in Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO TOLUENE?

You may be exposed to toluene from many sources, including drinking water, food, air, and consumer products. You may also be exposed to toluene through breathing the chemical in the workplace or during deliberate glue sniffing or solvent abuse. Automobile exhaust also puts toluene into the air. People who work with gasoline, kerosene, heating oil, paints, and lacquers are at the greatest risk of exposure. Printers are also exposed to toluene in the workplace. Because toluene is a common solvent and is found in many consumer products, you can be exposed to toluene at home and outdoors while using gasoline, nail polish, cosmetics, rubber cement, paints, paintbrush cleaners, stain removers, fabric dyes, inks, adhesives, carburetor cleaners, and lacquer thinners. Smokers are exposed to small amounts of toluene in cigarette smoke.

You can be exposed to toluene at some hazardous waste sites. EPA reported in 1998 that toluene was found in well water or surface water at 99% of the hazardous waste sites surveyed and in soil at 77% of the sites surveyed. If you live near a waste site and get your drinking water from a well, toluene may be in the water. Toluene vapors might also be present in the air.

Federal and state surveys do not show toluene to be commonly found in drinking water supplies. Toluene was found in about 1% of the groundwater sources (wells) at amounts lower than 2 parts per billion (ppb). It was found more frequently in surface water samples at similar concentrations. If toluene is in your drinking water you can be exposed by drinking the water or by eating cold foods prepared with the water. Evaporation during cooking tends to decrease the amount of toluene found in hot foods or water. Additional exposure will occur when you breathe in the toluene that evaporates from water while you shower, bathe, clean, or cook with the water.

The toluene level in the air outside your home is usually less than 1 ppm in cities and suburbs that are not close to industry. The toluene inside your house is also likely to be less than 1 ppm. The amount of toluene in food has not been reported, but is likely to be low. Traces of toluene were found in eggs that were stored in polystyrene containers containing toluene.

Unless you smoke cigarettes or work with toluene-containing products, you are probably exposed to only about 300 micrograms (μg) of toluene a day. A microgram is one-millionth of a gram. If you smoke a pack of cigarettes per day, you add another 1,000 μg to your exposure. People who work in places where toluene-containing products are used can be exposed to 1,000 milligrams of toluene a day when the average air concentration is 50 ppm and they breathe at a normal rate and volume. A milligram is one-thousandth of a gram.

More information on how you can be exposed to toluene can be found in Chapter 5.

1.4 HOW CAN TOLUENE ENTER AND LEAVE MY BODY?

Toluene can enter your body when you breathe its vapors or eat contaminated food or drink contaminated water. When you work with toluene-containing paints or paint thinners, or use nail polish or nail polish remover containing toluene, the toluene can also pass through your skin into your bloodstream. You are exposed to toluene when you breathe air containing toluene. When this occurs the toluene is taken directly into your blood from your lungs. Where you live, work, and travel and what you eat affects your daily exposure to toluene. Factors such as your age, sex, body composition, and health status affect what happens to toluene once it is in your body. After being taken into your body, more than 75% of the toluene is removed within 12 hours. It may leave your body unchanged in the air you breathe out or in your urine after some of it has been changed to other chemicals. Generally, your body turns toluene into less harmful chemicals such as hippuric acid. More information on how toluene can enter and leave your body can be found in Chapter 2.

1.5 HOW CAN TOLUENE AFFECT MY HEALTH?

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

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may

also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

A serious health concern is that toluene may have an effect on your brain. Toluene can cause headaches and sleepiness, and can impair your ability to think clearly. Whether or not toluene does this to you depends on the amount you take in, how long you are exposed, and your genetic susceptibility and age. Low to moderate, day-after-day exposure in your workplace can cause tiredness, confusion, weakness, drunken-type actions, memory loss, nausea, and loss of appetite. These symptoms usually disappear when exposure is stopped. You may experience some hearing and color vision loss after long-term daily exposure to toluene in the workplace. Researchers do not know if the low levels of toluene you breathe at work will cause any permanent effects on your brain or body after many years.

If you are exposed to a large amount of toluene in a short time because you deliberately sniff paint or glue, you will first feel light-headed. If exposure continues, you can become dizzy, sleepy, or unconscious. You might even die. Toluene causes death by interfering with the way you breathe and the way your heart beats. When exposure is stopped, the sleepiness and dizziness will go away and you will feel normal again. If you choose to repeatedly breathe in toluene from glue or paint thinners, you may permanently damage your brain. You may also experience problems with your speech, vision, or hearing, have loss of muscle control, loss of memory, poor balance, and decreased mental ability. Some of these changes may be permanent.

Toluene (at high levels) could possibly damage your kidneys. If you drink alcohol and are exposed to toluene, the combination can affect your liver more than either compound alone. Combinations of toluene and some common medicines like aspirin and acetaminophen may increase the effects of toluene on your hearing.

Some studies in people have shown reproductive effects, such as an increased risk of spontaneous abortions, from exposure to toluene in the workplace. However, other factors, such as exposure to other chemicals, smoking and alcohol use, may have affected the results of the studies, so it is not possible to say whether toluene has reproductive effects in people.

The effects of toluene on animals are similar to those seen in humans. The main effect of toluene is on the brain and nervous system, but animals exposed to moderate or high levels of toluene may also show harmful effects in their liver, kidneys, and lungs.

Studies in workers and animals exposed to toluene generally indicate that toluene does not cause cancer. The International Agency for Research on Cancer (IARC) and the Department of Health and Human Services (DHHS) have not classified toluene for carcinogenic effects. The EPA has determined that toluene is not classifiable as to its human carcinogenicity.

More information on the health effects of toluene in humans and animals can be found in Chapter 2.

1.6 HOW CAN TOLUENE AFFECT CHILDREN?

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

Children may breathe air contaminated with toluene by family use of glues, paints, or cleaning solvents, or by accidents involving products containing toluene. Toluene vapors are heavier than air and since young children are closer to the ground or floor because of their height, they may breathe more toluene than adults during accidental exposures. Older children and adolescents may be exposed to toluene if they breathe household products containing it to get high. Nursing mothers who breathe toluene in workplace air may transfer some toluene in breast milk to their infants. Toluene is not stored in the body. Toluene in the body either rapidly leaves or is turned into less harmful chemicals. Thus, nursing mothers, who do not currently work in jobs with

toluene and who do not deliberately breathe large amounts of toluene, are expected to transfer very little toluene in breast milk.

The effects of toluene on children have not been studied very much, but toluene is likely to produce the same types of effects on the brain and nervous system in children as it does in adults. Some older children and adolescents who have repeatedly breathed large amounts of toluene to get high have developed loss of muscle control, loss of memory, poor balance, and decreased mental ability. Some of these changes may last for a long time after toluene has left the body. Young animals exposed to toluene have shown changes in behavior, hearing loss, and chemical changes in their brains.

Human fetuses and newborn babies may be more sensitive to toluene than adults, because their bodies may not be as able to turn toluene into less harmful chemicals. Some animal studies suggest that young animals might be more susceptible to toluene effects on health, but, shortly after birth, human babies begin to develop the ability to turn toluene into less harmful chemicals. By the time children are 1–3 years of age, they may be equal to adults in this ability.

Some mothers who breathed large amounts of toluene during pregnancy to get high have had children with birth defects, including retardation of mental abilities and growth. Results from animal studies have found similar effects in new born animals that had mothers that breathed large amounts of toluene during pregnancy. However, when the animal mothers breathed small amounts of toluene during pregnancy, no birth defects were found in their newborn animals. When pregnant animals breathe small amounts of toluene during pregnancy, studies show that very little toluene reaches the developing fetus.

More information on the effects of toluene on children can be found in Chapter 2.

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

If your doctor finds that you have been exposed to significant amounts of toluene, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Families can reduce their risk of exposure to toluene by only using consumer products containing it (such as paints, glues, inks, and stain removers) in well ventilated areas. When not in use, toluene-containing products should be tightly covered to prevent evaporation into the air. Household chemicals should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers. Never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number next to the phone. Sometimes older children sniff household chemicals in an attempt to get high. Your children may be exposed to toluene by inhaling products containing it. Talk with your children about the dangers of sniffing chemicals.

See Chapter 5 for more information on how families can reduce the risk of exposure to toluene.

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

You can find out if you have been exposed to toluene by having your exhaled air, blood, and urine tested for toluene or its breakdown products. These tests may not be available at a doctor's office, but are easily done by special laboratories. To determine if you have been exposed to toluene, your blood and urine must be checked within 12 hours of exposure for the presence of toluene or its breakdown products. Several other chemicals are also changed to the same breakdown products as toluene in the body, so some of these tests are not specific for toluene. Other factors, such as your weight and body fat, your sex, and the exposure conditions, may also influence the amount of the chemicals in your urine. More information on testing for exposure to toluene can be found in Chapters 2 and 6.

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

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

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

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

The federal government has developed regulatory standards and guidelines to protect you from the possible health effects of toluene in the environment. OSHA has set a limit of 200 ppm of toluene for air in the workplace, averaged for an 8-hour exposure per day over a 40-hour work week. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends that toluene in workplace air not exceed 50 ppm, and NIOSH recommends that toluene in workplace air not exceed 100 ppm (both as average levels over 8 hours).

EPA has set a maximum contaminant level (MCL) for toluene in drinking water of 1 milligram per liter of water (1 mg/L). Any release of more than 1,000 pounds of this chemical to the

environment must be reported to the National Response Center. More information on federal and state government regulations and guidelines for toluene in air and water can be found in Chapter 7.

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

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: (404) 639-6359

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

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

2.2.1 Inhalation Exposure

Adverse effects on the nervous system are the critical effects of concern from inhalation exposure to toluene as evidenced by results from studies of workers acutely or chronically exposed to toluene in workplace air, studies of volunteers under controlled acute exposure conditions, and studies of chronic solvent abusers predominantly exposed to toluene. Observed effects include reversible neurological symptoms from acute exposure progressing from fatigue, headache, and decreased manual dexterity to narcosis with increasing exposure level, degenerative changes in white matter in chronic solvent abusers, and subtle changes in neurological functions including cognitive and neuromuscular performance, hearing, and color discrimination in chronically exposed workers. Studies of toluene-exposed animals provide supporting data showing changes in behavior, hearing loss, and subtle changes in brain structure, brain electrophysiology, and brain chemistry. Case reports of birth defects and developmental delays in children of mothers who abused solvents, including toluene, during pregnancy suggest that exposure to high levels of toluene may be toxic to the developing fetus. A number of developmental toxicity studies with rats, mice, and rabbits exposed to airborne toluene indicate that toluene is not a potent teratogenic agent at exposure levels below those inducing maternal toxicity, but can retard fetal growth and skeletal development and alter development of behavior in offspring.

2.2.1.1 Death

Limited data are available on toluene-associated deaths due to solvent abuse or occupational exposure and these studies do not indicate exposure concentrations. Paterson and Sarvesvaran (1983) reported on a teenager who died following an episode of glue sniffing. In Japan, a man died of cardiac arrest after painting a bathroom using a sealer containing 65% toluene (Shibata et al. 1994) and a woman died of adrenal hemorrhage after sniffing thinner containing 67% toluene (Kamijo et al. 1998). In Great Britain, approximately 80 deaths per year have been associated with solvent abuse (Anderson et al. 1985). Approximately half these cases were attributed to cardiac arrhythmias, central nervous system depression, asphyxia, and hepatic and renal failure (Anderson et al. 1982). Among the 52 cases with a toxicological report, 42 mentioned toluene(Anderson et al. 1982).

There are only a few animal inhalation studies that have examined the lethality of toluene, and there is evidence from an intermediate-duration study suggesting that mice may be more sensitive than rats. An inhalation LC_{50} value (concentrations causing death in of 50% of the animals) of 5,320 ppm has been reported for mice (Svirbely et al. 1943). In 14 to 15 week studies, exposure to 3,000 ppm toluene for 6.5 hours/day, 5 days/week, caused 80% mortality in male rats, 60% mortality in male mice, and 100% mortality in female mice, but no deaths among female rats (NTP 1990). Death also occurred among female mice exposed to 625 (10%), 1,250 (10%), and 2,500 (40%) ppm toluene (NTP 1990).

LOAEL values for deaths in the NTP (1990) study and the LC_{50} from the Svirbely et al. (1943) report are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Data are available pertaining to respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine and ocular effects in humans and animals after inhalation exposure to toluene. In addition, there are data on gastrointestinal, dermal, body weight, and other systemic effects in animals after inhalation exposure to toluene. All systemic effects are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. In humans, respiratory tract irritation is experienced from exposure to toluene. Irritation of the upper airways and degeneration of the nasal epithelium have been observed in animal studies.

Exposure of volunteers to 40 ppm of toluene for 6 hours did not produce statistically significant differences in the results of tests measuring nasal mucus flow and lung function or in subjective evaluations of air quality, but irritation of the nose was noted at 100 ppm (Andersen et al. 1983). No changes in lung function were reported for volunteers exposed to 100 ppm toluene for 6 hours, 30 minutes of which were spent exercising (Rahill et al. 1996). Individuals exposed to 800 ppm toluene for 3 hours (von Oettingen et al. 1942) or 1,862 ppm for 2 hours (Meulenbelt et al. 1990) had no self-reported respiratory effects. However, irritation of the nose and throat was reported in printers exposed to 100 ppm toluene for 6.5 hours (Baelum et al. 1985), and in volunteers exposed to 200 ppm toluene for 7–8 hours (Carpenter et al. 1944). Eight workers from a print factory exposed to <200 ppm toluene for

Table 2-1. Levels of Significant Exposure to Toluene - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE								
Death								
1	Mouse (Swiss-Webster)	7 hr					5320 (LC_{50})	Svirbely et al. 1943
Systemic								
2	Human	6 hr	Resp	40	M	100 M (irritation of the nose)		Andersen et al. 1983
			Ocular	40	M	100 M (irritation of the eyes)		
3	Human	6.5 hr	Resp			100 M (irritation of the nose and throat)		Baelum et al. 1985
			Ocular			100 M (irritation of the eyes)		
4	Human	7-8 hr	Resp			200 M (mild throat irritation)		Carpenter et al. 1944
			Ocular			200 M (eye irritation)		
5	Human	3 hr	Resp	1862	M			Meulenbelt et al. 1990
			Cardio			1862 M (sinus bradycardia)		
			Hemato			1862 M (elevated anion gap)		
			Hepatic	1862	M			
			Ocular			1862 M (mucosal irritation)		
6	Human	6.5 hr	Renal	102	M			Nielsen et al. 1985
7	Human	6 hr/d	Resp	100				Rahill et al. 1996
8	Human	3 hr	Resp	800				von Oettingen et al. 1942
			Cardio	800				
			Hemato	800				

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL: Less serious (ppm)	LOAEL: Serious (ppm)	Reference
9	Rat (Sprague-Dawley)	48 hr	Hemato		2000 M (increased hematocrit and blood glucose)		Tahti et al. 1983
			Hepatic		2000 M (increased serum ALT and AST)		
			Bd Wt		2000 M (body weight decrease 10%)		
10	Rat	7 d 8 hr/d	Hepatic		795 F (increased liver weight 12%, increased smooth and rough endoplasmic reticulum)		Ungvary et al. 1982
11	Rat (Wistar)	6 hr	Hepatic		4000 (increased CYP2E1 and decreased CYP 2 C11 in liver)		Wang et al. 1996
12	Mouse	7 d 8 hr/d	Hepatic		795 F (increased liver weight 11% and cytochrome P-450 30%)		Ungvary et al. 1982
13	Dog	1 hr	Hemato	200	500 (decreased leukocytes)		Hobara et al. 1984a
14	Rabbit	7 d 8 hr/d	Hepatic		795 F (increased liver weight 14%, cytochrome P-450-35%, and cytochrome b5-25%)		Ungvary et al. 1982
	Immunological/Lymphoreticular						
15	Rat (Sprague-Dawley)	Gd 7-17 6 hr/d			600 F (significant decrease thymus weights in dams)		Ono et al. 1995
16	Mouse (CD-1)	3 hr		1 F	2.5 F (increased susceptibility to infections)		Aranyi et al. 1985

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)		LOAEL Serious (ppm)	Reference
Neurological									
17	Human	6 hr		40[b]	M	100	M	(headaches, dizziness, intoxication)	Andersen et al. 1983
18	Human	6.5 hr				100	M	(intoxication, dizziness, decreased manual performance and color perception)	Baelum et al. 1985
19	Human	7 hr				75		(dose-related impairment of performance on recognition, pattern memory, and one-hole test results)	Echeverria et al. 1991
20	Human	4 hr		80	M				Iregren 1986
21	Human	28-41 min		1250	M			(color vision impairment)	Muttray et al. 1999
22	Human	6 hr				100		(decreased perfomance on neuropsychological tests)	Rahill et al. 1996
23	Human	3 or 8 hr				200		(drowsiness and headache)	von Oettingen et al. 1942
24	Monkey (Cynomolgus)	50 min		1000	F	2000	F	(cognitive and motor skills impaired)	Taylor and Evans 1985
25	Rat	8 hr				900	M	(altered patterns of sleep and wakefulness)	Arito et al. 1988
26	Rat (Fischer- 344)	2 hr				110	M	(decreased REM sleep)	Ghosh et al. 1989

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
27	Rat (Fischer- 344)	2 hr			110 M (changes in sleep pattern)		Ghosh et al. 1990
28	Rat (Wistar)	4 hr			2000 M (increased lever presses during exposure)	4000 M (decreased shock avoidance behavior)	Harabuchi et al. 1993
29	Rat (Long- Evans)	1 hr		2500 M	5000 M (increased locomotor activity)		Hinman 1987
30	Rat (Sprague-Dawley)	10 d 16 hr/d			1000 M (loss of auditory sensitivity)		Johnson 1992
31	Rat (Sprague-Dawley)	8 d 14 hr/d			1400 M (hair loss in cochleae)		Johnson and Canlon 1994
32	Rat (Sprague-Dawley)	2 wk 5 d/wk 16 hr/d			1000 M (diminished auditory response)		Johnson et al. 1988
33	Rat	20 min			1000 (increased dopamine in the cerebellum and striatum and norepinephrine and 5-hydroxytryptamine in the cerebellum and cortex)		Kim et al. 1998
34	Rat (Wistar)	4 hr			125 M (a temporary decline in conditioned avoidance response)		Kishi et al. 1988
35	Rat	14 d 1 hr/d			1500 (nystagmus)		Larsby et al. 1986

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
36	Rat (Fischer- 344)	6 h/d, for 3 or 7 d			1000 M (decreased GFAP in thalamus and increased corticosterone)		Little et al. 1998
37	Rat (Fischer- 344)	0, 1600, 3200 ppm for 4 hr			1600 M (reduced lever press response accuracy)		Miyagawa et al. 1998
38	Rat (CD)	4 hr			810 M (decr lift reflex, vertical bar placing, and horizontal rod grasping)		Mullin and Krivanek 1982
39	Rat (Fischer- 344)	7 d 8 hr/d			1929 M (diminished auditory response)		Pryor et al. 1991
40	Rat (Long- Evans)	30 min			8000 M (changes in sensory-evoked potentials, brainstem auditory-evoked responses and flash-evoked potentials and oscillations in the visual cortex)		Rebert et al. 1989a
41	Rat (Fischer- 344)	30 min			500 M (changes in flash-evoked and somatosensory-evoked potentials)		Rebert et al. 1989b
42	Rat	4 hr			1000 M (sleep pattern disturbances- reduced slow wave sleep and increased paradoxical phase)		Takeuchi and Hisanega 1977

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
43	Rat	7+3 d 6 hr/d			80 M (decreased dopamine concentration and noradrenaline utilization)		Von Euler et al. 1989b
44	Rat	2-4 hr			480 (decreased performance in rewarded task)		Wood et al. 1983
45	Mouse CFW (ChasRiver Swiss) albino	30 min		250	500 (increased locomotor activity)		Bowen and Balster, 1998
46	Mouse (NS)	0.5-3 hr			2600 M (central nervous system depression)		Bruckner and Peterson 1981a
47	Mouse (ICR)	8x/d 5 min			12000 M (narcosis)		Bruckner and Peterson 1981b
48	Mouse (C57BL/6N)	5 d 72 min/d		100 M	1000 M (increased locomotor activity)		Bushnell et al. 1985
49	Mouse (CD-1)	Gd 7-16 7 hr/d		200 F	400 F (increased total dehydrogenase activity in brain)		Courtney et al. 1986
50	Mouse (CBA/CA; C57BL/6J)	7 d 12 hr/d			1000 F (accelerated hearing loss in genetically predisposed mice)		Li et al. 1992
51	Mouse ddy	500 ppm for 8 hr		500 M			Matsuoka et al 1997
52	Mouse (CD-1)	6x 1 hr/x		300 M	560 M (increased activity)		Wood and Colotla 1990

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
Reproductive										
53	Rat (Wistar)	7 d 8 hr/d				3000 F	(structural variations in antral follicles in ovary)			Tap et al. 1996
54	Rat (Wistar)	Gd 9-21 6 hr/d		1200						Thiel and Chahoud 1997
55	Rabbit	Gd 7-20 24 hr/d		133	F	266	(4/8 dams aborted)			Ungvary and Tatrai 1985
Developmental										
56	Rat CFY	gd 1-8, 24 hr/d						399	(5/14 dams died, increased incidence of fetuses with skeletal retardation)	Hudak and Ungvary 1978
57	Rat CFY	gd 9-14, 24 hr/d						399	(2/21 dams died, increased incidence of fetuses with skeletal anomalies)	Hudak and Ungvary 1978
58	Rat (Crl:CD (SD) BR VAF/Plus)	Gd 6-15 6 hr/d		750		1500	(decreased fetal bodyweight)	3000	(decreased fetal body weight and increased incidence of fetuses with unossified sternebrae)	Huntingdon Research Centre 1992b
59	Rat (Crl:CD BR VAF/Plus)	Gd 6-15 6 hr/d						3500	(20% decrease in fetal body weight, total absorption at higher exposure levels)	Huntington Research Centre 1992a
60	Rat (Sprague-Dawley)	Gd 7-17 6 hr/d		600		2000	(decreased fetal body weight)			Ono et al. 1995
61	Rat (Wistar)	Gd 9-21 6 hr/d		600		1000	(decreased body weight of fetus and delayed vaginal opening)	1200	(significantly increased postnatal/preweening mortality in offspring)	Thiel and Chahoud 1997

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL: Less serious (ppm)	LOAEL: Serious (ppm)	Reference
62	Mouse (CD-1)	Gd 7-16 7 hr/d			200 (increased number of litters with fetuses with dilated renal pelvis)		Courtney et al. 1986
63	Mouse (CD-1)	Gd 7-16 7 hr/d			400 (increased activity of brain lactate dehydrogenase in 21-day-old weanling pups)		Courtney et al. 1986
64	Mouse CFLP	gd 6-13, 24 hr/d			133 (decreased fetal body weight)	399 (maternal mortality)	Hudak and Ungvary 1978
65	Mouse (CD-1)	Gd 12-17 3x/d 60 min		400		2000 (performance deficits in tests of reflexes, muscle strength and motor coordination in offspring)	Jones and Balster, 1997
66	Mouse	gd 6-15 3-4 hr/d		133	266 (decreased fetal body weight and retardation of fetal skeletal development)		Ungvary and Tatrai 1985
67	Rabbit	gd 6-18 6 hr/d		500			Klimisch et al. 1992
68	Rabbit	Gd 7-20 14 d 24 hr/d		133 F		266 F (4/8 does aborted)	Ungvary and Tatrai 1985
INTERMEDIATE EXPOSURE							
Death							
69	Rat (Fischer- 344)	15 wk 5 d/wk 6.5 hr/d				3000 M (8/10 or 80% died)	NTP 1990

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
70	Mouse (B6C3F1)	14 wk 5 d/wk 6.5 hr/d					625 F (1/10 died)	NTP 1990
							3000 M (6/10 died)	
	Systemic							
71	Human	2-14 mo 8 hr/d	Hepatic	167	F			Seiji et al. 1987
72	Rat (CD)	95 d 7 d/wk 6 hr/d	Endocr	2000				API 1985
			Dermal	2000				
			Ocular	2000				
			Bd Wt	2000				
73	Rat (Fischer- 344)	42 d 5 d/wk 6 hr/d	Bd Wt	1000	M			API 1997
74	Rat (albino)	8 wk 5 d/wk 70 min/d	Resp	12000	M			Bruckner and Peterson 1981b
			Cardio	12000	M			
			Hepatic			12000 M (decreased liver weight-11%, elevated liver enzymes in serum)		
			Renal			12000 M (decreased kidney weight-27%)		
			Bd Wt				12000 M (20% reduction in body weight gain)	
75	Rat (Sprague-Dawley)	30 d 24 hr/d	Hepatic	320	M			Kyrklund et al. 1987
			Bd Wt			320 M (10% decreased body weight)		

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
76	Rat (Fischer- 344)	13 wk 5 d/wk 15-35 min, 4-9 x/d	Bd Wt					8000 M	(23% decreased body weight gain)	Mattsson et al. 1990
77	Rat (Fischer- 344)	15 wk 5 d/wk 6.5 hr/d	Resp	1250		2500	(9-15% increased relative lung weight)			NTP 1990
			Cardio	1250		2500	(6-11% increased relative heart weight)			
			Gastro	3000						
			Hemato	625	F	1250 F	(decreased leukocytes)			
				3000	M					
			Hepatic	625	M	1250 M	(9% increase in relative liver weight)			
				1250	F	2500 F	(16% increase in relative liver weight)			
			Renal	625		1250	(increased relative kidney weights)			
			Endocr	3000						
			Bd Wt	1250		2500	(final body weights 15% lower than controls in males and females)	3000 M	(final body weights 25% lower than controls)	
78	Rat (Sprague-Dawley)	21 d 6 hr/d	Ocular	600		2000 F	(lacrimation)			Ono et al. 1996
79	Rat (Sprague-Dawley)	90 d 6 hr/d	Hemato	2000	M					Ono et al. 1996
			Renal	600	M	2000 M	(increase in kidney weights, necrosis of kidney tubules)			
			Bd Wt	2000	M					

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
80	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d	Resp		30 F (submucosal edema of tracheal epithelium)		Poon et al. 1994
			Hemato	300			
			Hepatic	30	300 (significantly increased serum alkaline phosphatase in males & variation hepatocellular size in females)		
			Renal	300			
			Endocr		30 F (mild reduction in follicle size in thyroid)		
81	Rat (Fischer- 344)	23 wk 7 d/wk 8 hr/d 60, 30, 15 min/hr	Bd Wt		2200 M (decreased body weight gain)		Pryor 1991
82	Rat (Fischer- 344)	11 wk 7 d/wk 8 hr/d	Bd Wt		2000 M (decreased body weight gain)		Pryor 1991
83	Rat (NS)	5 wk 5 d/wk 7 hr/d	Resp		600 (irritation of the lung)	2500 (pulmonary lesions)	von Oettingen et al. 1942
			Hemato	600	2500 (transient decrease in leukocytes)		
			Hepatic	5000			
			Renal		600 (renal casts)		
			Endocr	5000			

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
84	Mouse (ICR)	8 wk 3 hr/d 5 d/wk	Resp	4000	M			Bruckner and Peterson 1981b
			Cardio	4000	M			
			Hepatic			4000 M (increased relative liver weight, elevated serum glutamic oxaloacetic transaminase)		
			Renal	4000	M			
			Bd Wt			4000 M (significant decrease, 5-10%, in body weight gain)		
85	Mouse (ICR)	8 wk 5 d/wk 70 min/d	Resp	12000	M			Bruckner and Peterson 1981b
			Cardio	12000	M			
			Hepatic			12000 M (decreased liver weight)		
			Renal			12000 M (decreased kidney weight)		
			Bd Wt			12000 M (20% reduction in body weight)		
86	Mouse	20 d 6 hr/d	Hemato			10 M (decreased white blood cells and thrombocytes)		Horiguchi and Inoue 1977
			Bd Wt	1000	M			
87	Mouse	30 d 24 hr/d	Hepatic			150 F (increased liver weight-9.6%)		Kjellstrand et al. 1985

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
88	Mouse (B6C3F1)	14 wk 5 d/wk 6.5 hr/d	Resp			100 F (12% increase in relative lung weight)		NTP 1990
				1250	M	2500 M (5% increase in relative lung weight)		
			Cardio	1250	F	2500 F (14% increase in relative heart weight)		
				2500	M			
			Gastro	2500				
			Hemato	2500				
			Hepatic	100	F	625 F (6% increase in relative liver weight)		
				625	M	1250 M (9% increase in relative liver weight)		
			Renal	625	F	1250 F (7% increase in relative kidney weight)		
				2500	M			
			Endocr	2500				
			Bd Wt			100 F (13% lower body weight than controls)		
				1250	M	2500 M (12% lower body weight than controls)		
Immunological/Lymphoreticular								
89	Rat (Fischer- 344)	42 d 5 d/wk 6 hr/d		1000	M			API 1997
90	Rat (Fischer- 344)	15 wk 5 d/wk 6.5 hr/d		3000				NTP 1990
91	Rat (Sprague-Dawley)	90 d 6 hr/d		600		2000 M (decrease in thymus weights)		Ono et al. 1996

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
92	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d		300			Poon et al. 1994
93	Rat (NS)	5 wk 5 d/wk 7 hr/d		5000			von Oettingen et al. 1942
94	Mouse (CD-1)	4 wk 5 d/wk 3 hr/d		1 F	2.5 F (increased susceptibility to infections)		Aranyi et al. 1985
95	Mouse (B6C3F1)	14 wk 5 d/wk 6.5 hr/d		2500			NTP 1990
	Neurological						
96	Rat (Fischer- 344)	42 d 5 d/wk 6 hr/d			100 M (changes in GFAP levels in brain)	3000 M (overt signs of neurotoxicity)	API 1997
97	Rat	3 wk 5 d/wk 8 hr/d			900 M (prolonged slow-wave sleep and paraoxical sleep latencies)		Arito et al. 1988
98	Rat	4 wk 8 hr/d			50 M (changes in neurotransmitter-related parameters)		Bjornaes and Naalsund 1988
99	Rat (Long- Evans)	4 wk 5 d/wk 6 hr/d			1000 M (loss of hair cells in organ of Corti)		Campo et al. 1997
100	Rat (Long- Evans)	6h/d, 5 d/wk, 4 wk			1750 (hearing damage)		Campo et al. 1998

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
101	Rat (Wistar)	30 d 15 min/d			35000 M (increased latency of initial response of escape and latency to escape)		Castilla-Serna et al. 1991
102	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d		40 M	80 M (decrease in wet weight & increase in dopamine binding in caudate-putamen)		Hillefors-Berglund et al. 1995
103	Rat (Wistar)	30 d 24 hr/d		200 M	400 M (reduced noradrenaline or dopamine in selected areas of the brain)		Ikeda et al. 1986
104	Rat (Wistar)	6 mo 5 d/wk 6 hr/d				1500 M (signficantly fewer neurons in hippocampus)	Korbo et al. 1996
105	Rat (Sprague-Dawley)	30 d 24 hr/d			320 M (decreased phospholipids in cerebral cortex; decreased weight of brain and cerebral cortex)		Kyrklund et al. 1987
106	Rat (Long- Evans)	4 wk 5 d/wk 6 hr/d			2000 M (loss of hearing)		Lataye and Campo 1997
107	Rat (Wistar)	ppd 3-56 5 d/wk 15 min/d			10000 M (increased righting reflex latency and decreased hypnotic latency over weeks 5-8)		Lorenzana-Jimenez and Salas 1990

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
108	Rat (Fischer- 344)	13 wk 5 d/wk 15-35 min, 4-9 x/d			8000 M (decreased auditory brainstem response & flash-evoked potential & other neurobehavioral changes)		Mattsson et al. 1990
109	Rat (Fischer- 344)	50 d 24 hr/d		600 M			Miyagawa et al. 1995
110	Rat (Fischer- 344)	15 wk 5 d/wk 6.5 hr/d		1250	2500 (ataxia, increased relative brain weight)		NTP 1990
111	Rat (Fischer- 344)	11 wk 7 d/wk 8 hr/d			2273 M (gait and stride abnormalities, impaired hearing)		Pryor 1991
112	Rat (Fischer- 344)	23 wk 7 d/wk 8 hr/d 60, 30, or 15 min/hr			2200 M (gait and stride abnormalities; diminished auditory response)		Pryor 1991
113	Rat (Fischer- 344)	9 wk 7 d/wk 14 hr/d			1200 M (hearing loss, motor disturbances)		Pryor and Rebert 1992
114	Rat (Fischer- 344)	5 wk 7 d/wk 14 hr/d			1200 M (high-frequency hearing loss, more severe in rats exposed as weanlings)		Pryor et al. 1984a
115	Rat (Fischer- 344)	16 wk + 5 wk 7 d/wk 14 hr/d		700 M	1000 M (diminished auditory response)		Pryor et al. 1984b

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
116	Rat (Sprague-Dawley)	13 wk 8 hr/d		1000 M			Tahti et al. 1983
117	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d			80 M (increased dopamine D2 receptors)		Von Euler et al. 1993
118	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d			80 (increase in serum prolactin levels)		Von Euler et al. 1994
119	Rat (NS)	5 wk 5 d/wk 7 hr/d		600		2500 (incoordination)	von Oettingen et al. 1942
120	Rat (Long- Evans)	3 wk 2x/wk 2 hr/d			178 M (increased nose poking)		Wood and Cox 1995
121	Mouse (B6C3F1)	14 wk 5 d/wk 6.5 hr/d		2500			NTP 1990
	Reproductive						
122	Rat (CD)	95 d 7 d/wk 6 hr/d		2000			API 1985
123	Rat (Fischer- 344)	15 wk 5 d/wk 6.5 hr/d		1250 M 3000 F	2500 M (15% increased testis weight)		NTP 1990
124	Rat (Sprague-Dawley)	90 d 6 hr/d			600 M (slightly decreased (13%) sperm count)	2000 M (significantly decreased (26%) sperm count and decrease (15%) in wts of epididymes, but no effect on indices of fertility)	Ono et al. 1996

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
125	Mouse (CD-1)	8 wk 5 d/wk 6 hr/d		400	M			API 1981
126	Mouse (B6C3F1)	14 wk 5 d/wk 6.5 hr/d		2500				NTP 1990
Developmental								
127	Rat CFY	gd 1-21, 8hr/d				266 (increased incidence of fetuses with skeletal retardation)		Hudak and Ungvary 1978
128	Rat (Wistar)	ppd 1-28 12 hr/d				100 (decreased growth of hippocampus)		Slomianka et al. 1990
129	Rat (Wistar)	ppd 1-28 12 hr/d				500 M (reversible decrease in growth of hippocampus)		Slomianka et al. 1992
CHRONIC EXPOSURE								
Systemic								
130	Human	NS	Renal	80	M	106 M (urine albumin increased)		Askergren et al. 1981a
131	Human	>3 yr	Hemato	600				Banfer 1961
132	Human	>18 months 2-8 hr/d	Resp	200	M			Guzelian et al. 1988
			Hepatic			200 M (elevated alanine aminotransferase to aspartate aminotransferase ratios, fatty infiltration)		

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
133	Human	>3 yr	Hemato	100	F			Matsushita et al. 1975
			Hepatic	100	F			
134	Human	16 +/- 13 years	Renal	44				Stengel et al. 1998
135	Human	25 yr (median) 0.5-37 yr	Endocr			36 M (thyroid stimulating hormone levels were inversely proportional to cumulative toluene exposure)		Svensson et al. 1992a
136	Human	3-39 yr	Hepatic			29 M (increased levels of alkaline phosphatase)		Svensson et al. 1992b
137	Human	>10 yr	Hemato			110 (increased leukocytes)		Tahti et al. 1981
138	Human	NS	Hemato	24.7				Ukai et al. 1993
			Hepatic	24.7				
139	Human	73-96 mo	Hemato			41 (significant decrease in lymphocytes)		Yin et al. 1987
140	Rat (Fischer- 344)	106 wk 5 d/wk 6 hr/d	Resp	300				CIIT 1980
			Cardio	300				
			Hemato			100 (decreased hematocrit)		
			Hepatic	300				
			Renal	300				
			Bd Wt	300				

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
141	Rat (Fischer- 344)	2 yr 5 d/wk 6.5 hr/d	Resp		600 (nasal inflammation, degeneration of olfactory and nasal respiratory epithelium)		NTP 1990
			Cardio	1200			
			Gastro	1200			
			Hemato	1200			
			Musc/skel	1200			
			Hepatic	1200			
			Renal		600 (increased severity of nephropathy)		
			Endocr	1200			
			Bd Wt	1200			
142	Rat (Fischer- 344)	15 mo 5 d/wk 6.5 hr/d	Resp		600 (mild-to-moderate degeneration of the olfactory and respiratory epithelium)		NTP 1990
			Hemato	1200			
			Hepatic	1200			
143	Mouse (B6C3F1)	2 yr 5 d/wk 6.5 hr/d	Resp	1200			NTP 1990
			Cardio	1200			
			Gastro	1200			
			Hemato	1200			
			Musc/skel	1200			
			Hepatic	1200			
			Renal	1200			
			Endocr	1200			
			Bd Wt	1200			

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
144	Mouse (B6C3F1)	15 mo 5 d/wk 6.5 hr/d	Resp	600	F	1200 F (minimal hyperplasia of the bronchial epithelium)		NTP 1990
			Hepatic	1200	M			
Immunological/Lymphoreticular								
145	Human	13 yr (average)		1170	M			Pelclova et al. 1990
146	Human	16 +/- 13 yr				44 (increased IgE levels in blood)		Stengel et al. 1998
147	Human	73-96 mo				41 (significantly decreased lymphocytes and increased eosinophils)		Yin et al. 1987
148	Rat (Fischer- 344)	2 yr 5 d/wk 6.5 hr/d		1200				NTP 1990
149	Mouse (B6C3F1)	2 yr 5 d/wk 6.5 hr/d				120 M (increased incidence of pigmentation of the spleen)		NTP 1990
				1200	F			
Neurological								
150	Human	12-14 yr				97 M (increased wave latencies for BAEPs)		Abbate et al. 1993
151	Human	4.9 yr (average)				90.9 (statistically significant performance deficits on neurobehavioral tests)		Boey et al. 1997
152	Human	5.7 yr				88 F (statistically significant performance deficits on neurobehavioral tests)		Foo et al. 1990

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
153	Human	>18 mo 2-8 hr/d			200 M (mild intoxication)		Guzelian et al. 1988
154	Human	1-25 yr			122 M (hearing loss)		Morata et al. 1997
155	Human	1-36 yr			83 M (lowered coefficient of variation in electrocardiographic R-R intervals and maximal motor and sensory nerve conduction velocities in median nerve)		Murata et al 1993
156	Human	4-43 yr (median= 29 yr)			140 M (increased incidenec of self-reported neurological symptoms)		Orbaek and Nise 1989
157	Human	21.4 yr (average) range 4-30 yr			50 (increased wave latency of visual evoked potentials)		Vrca et al. 1995
158	Human	21.6 yr (range 4-30 yr)			50 (increased latency of BAEPs and decreased latency of visual evoked potentials)		Vrca et al. 1997a
159	Human	73-96 mo			41 (headaches, dizziness)		Yin et al. 1987
160	Human	17 yr (average)			35[c] (increased color confusion index)		Zavalic et al. 1998a, c
161	Human	16.8 +/- 5.94 yr			120 (increased color confusion index)		Zavalic et al. 1998b

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL				Reference
					Less serious (ppm)		Serious (ppm)		
162	Rat (Fischer- 344)	2 yr 5 d/wk 6.5 hr/d		1200					NTP 1990
163	Mouse (B6C3F1)	2 yr 5 d/wk 6.5 hr/d		1200					NTP 1990
	Reproductive								
164	Human	6 yr		150	F				Ng et al. 1992a
165	Human	10 yr					88	(increased incidence of spontaneous abortions (12.4/100) compared to 2 control groups (2.9/100 and 4.5/100))	Ng et al. 1992b
166	Rat (Fischer- 344)	106 wk 5 d/wk 6 hr/d		300					CIIT 1980
167	Rat (Fischer- 344)	2 yr 5 d/wk 6.5 hr/d		1200					NTP 1990

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
168	Mouse (B6C3F1)	2 yr 5 d/wk 6.5 hr/d		1200			NTP 1990

[a]The number corresponds to entries on Figure 2-1.
[b]Used to derive an acute inhalation minimal risk level (MRL); concentration was adjusted to a continuous exposure basis (40 ppm x 5d/7d x 8hr/24hr = 9.5 ppm) and divided by an uncertainty factor of 10 (for human variability), resulting in an MRL of 1 ppm (3.8 mg/m3).
[c]Used to derive chronic inhalation MRL; concentration was adjusted to a continuous exposure basis (35 ppm x 5d/7d x 8hyr/24hr = 8.3 ppm) and divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability), resulting in an MRL of 0.08 ppm (0.3 mg/m3).

ALT = alanine amino transferase; AST = aspartame aminotransferase; BAEP = brainstem auditory evoked potential; Bd Wt = body weight; Cardio - cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; GFAP = glial fibrillary acidic protein; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; ppd = post-partum day; Resp = respiratory; wk = week(s); yr = year(s); x = times

Figure 2-1. Levels of Significant Exposure to Toluene - Inhalation

Acute (≤14 days)

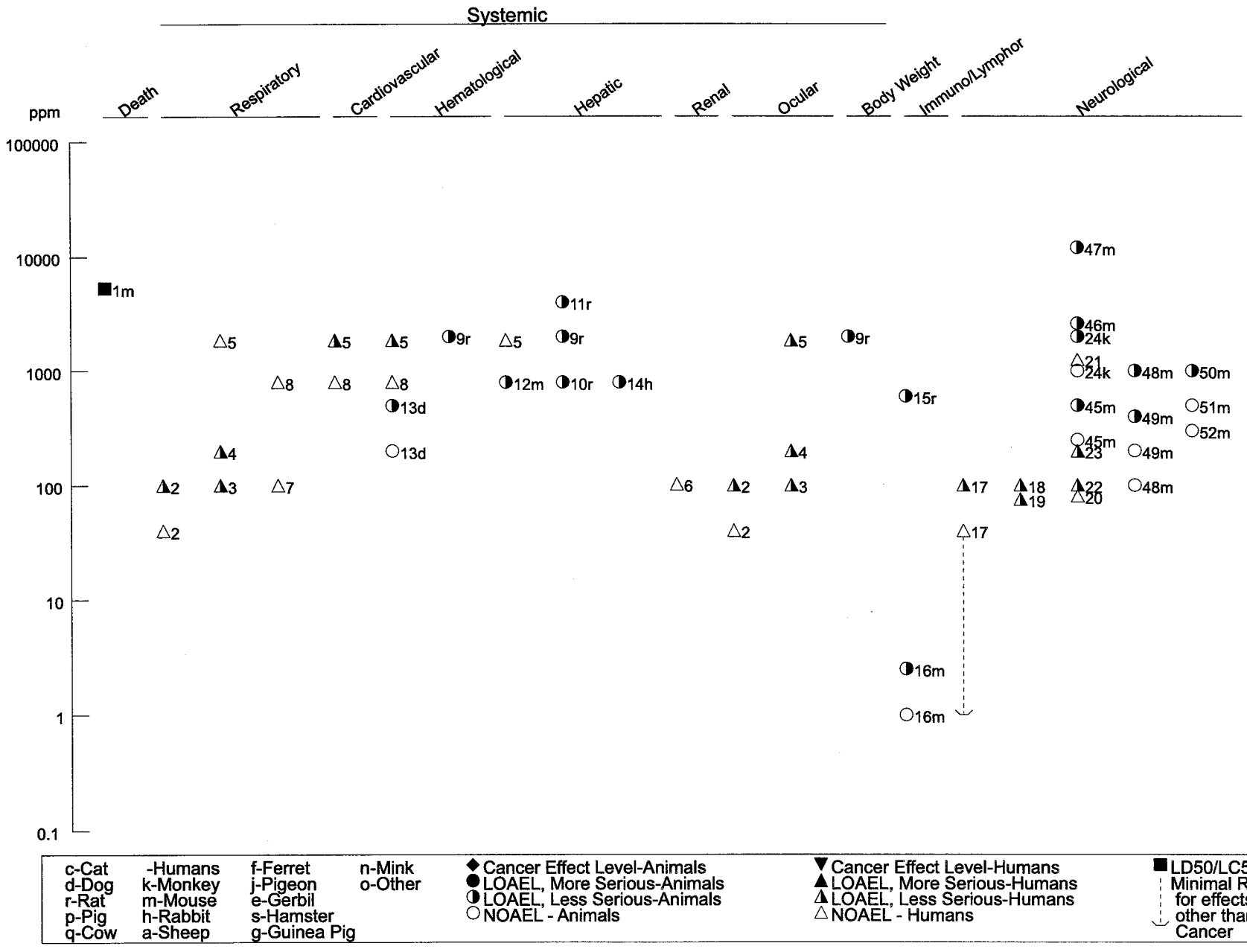


Figure 2-1. Levels of Significant Exposure to Toluene - Inhalation (continued)

Acute (≤14 days)

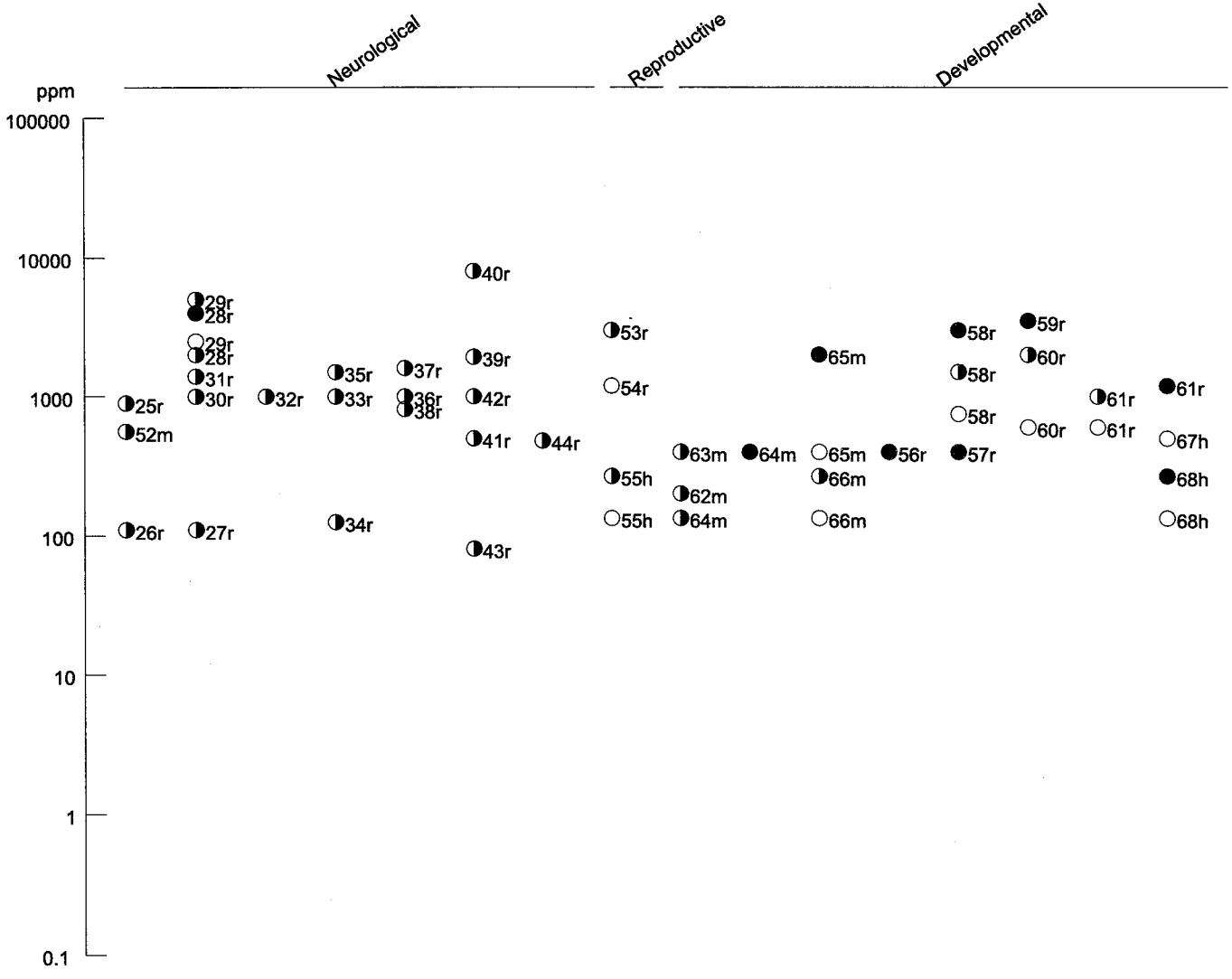


Figure 2-1. Levels of Significant Exposure to Toluene - Inhalation (continued)

Intermediate (15-364 days)

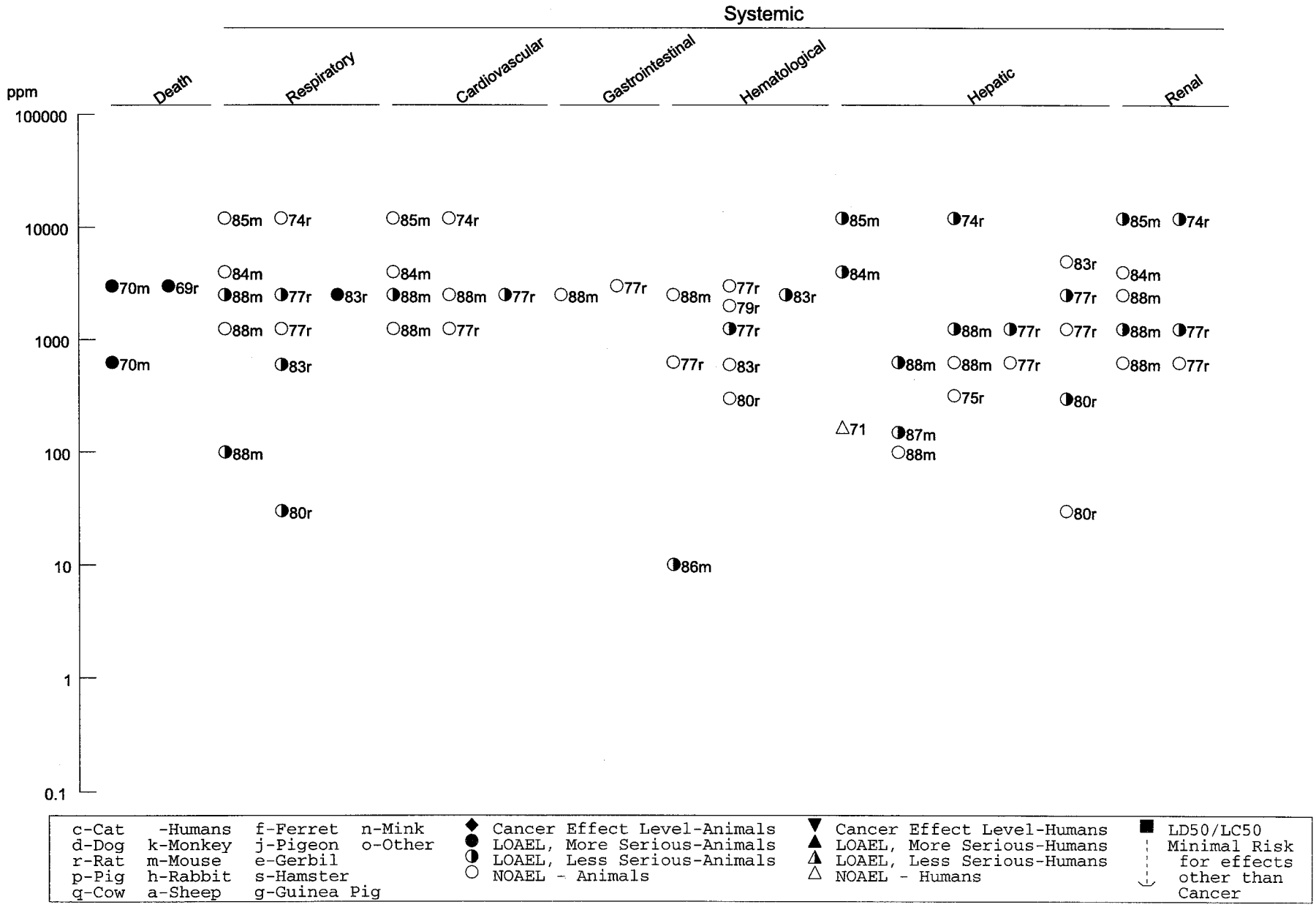


Figure 2-1. Levels of Significant Exposure to Toluene - Inhalation (continued)

Intermediate (15-364 days)

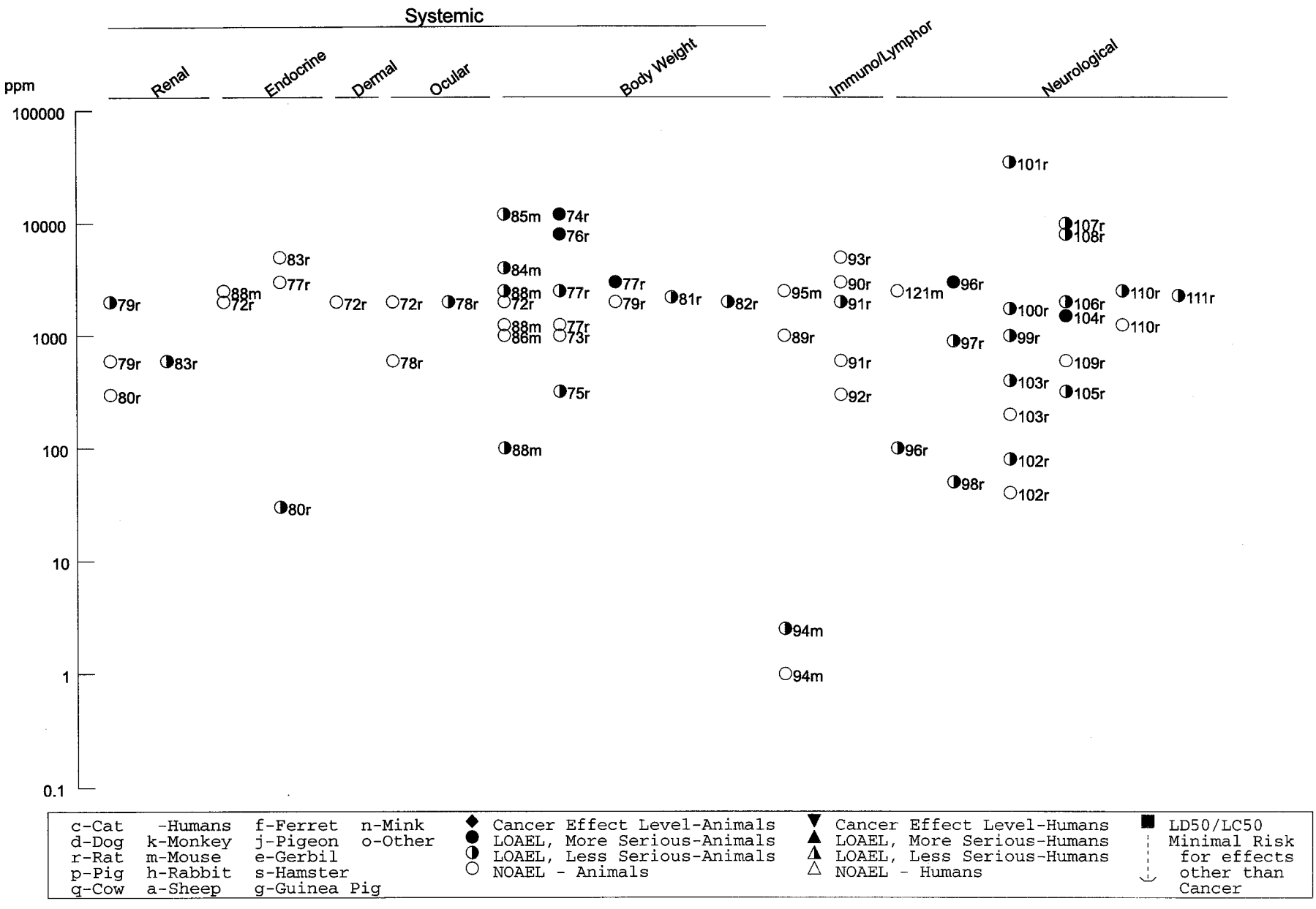
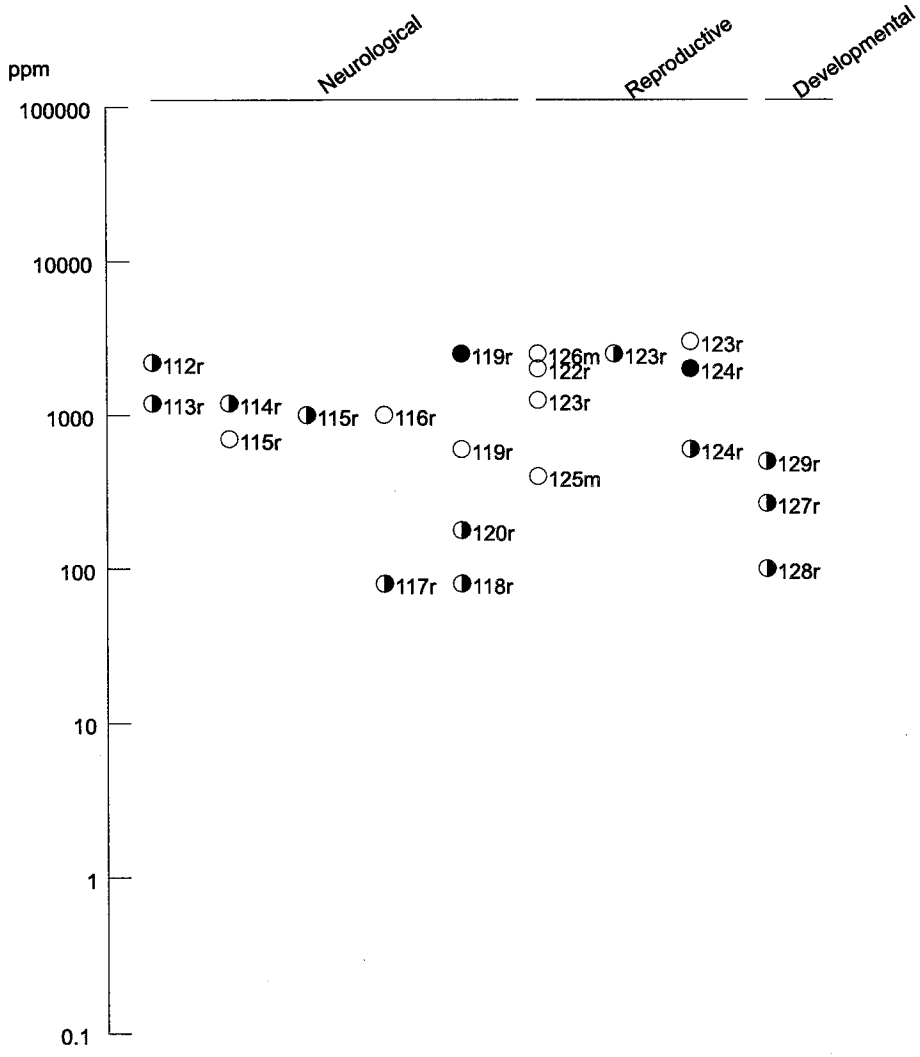


Figure 2-1. Levels of Significant Exposure to Toluene - Inhalation (continued)

Intermediate (15-364 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 2-1. Levels of Significant Exposure to Toluene - Inhalation (continued)

Chronic (≥365 days)

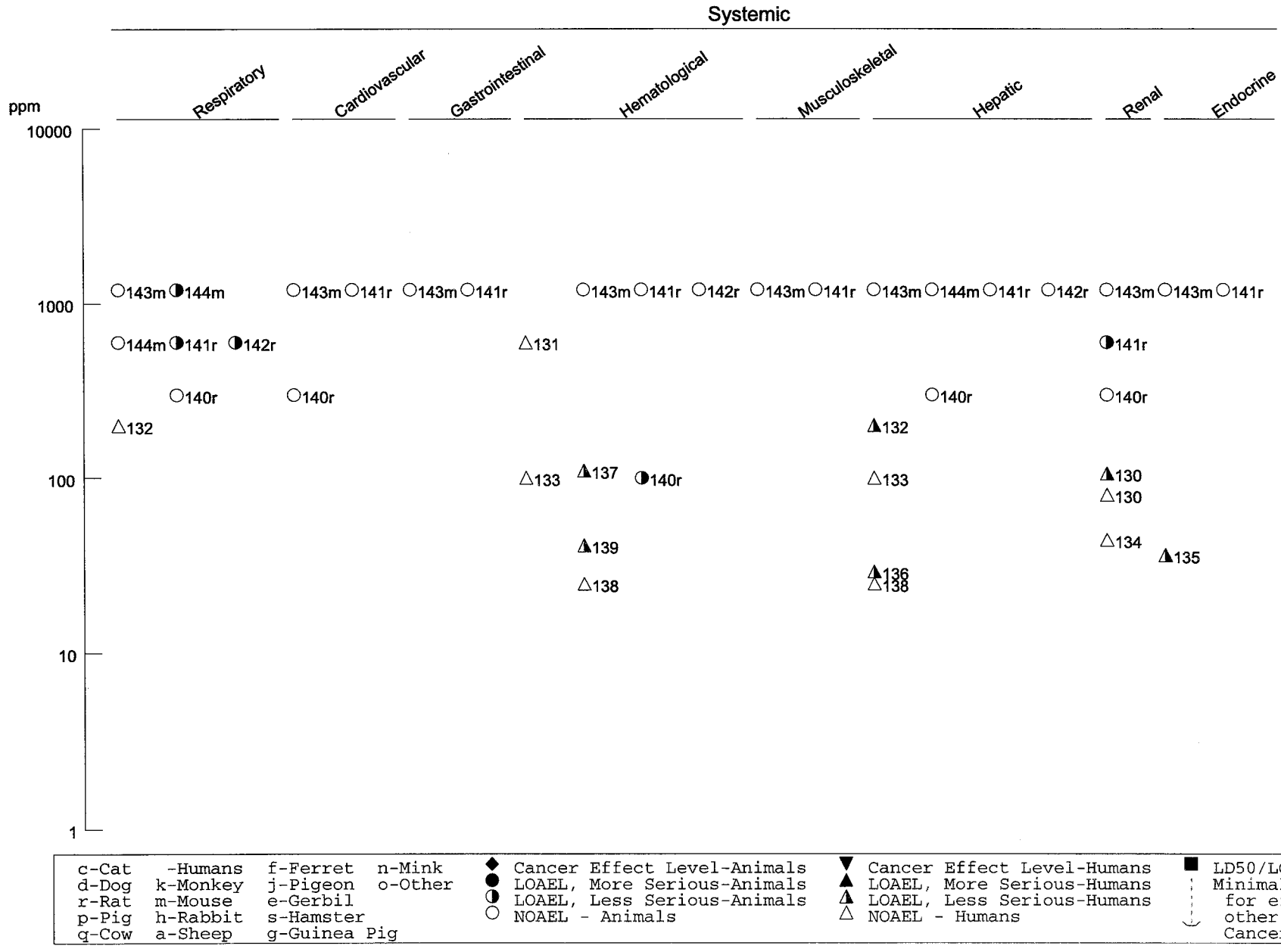
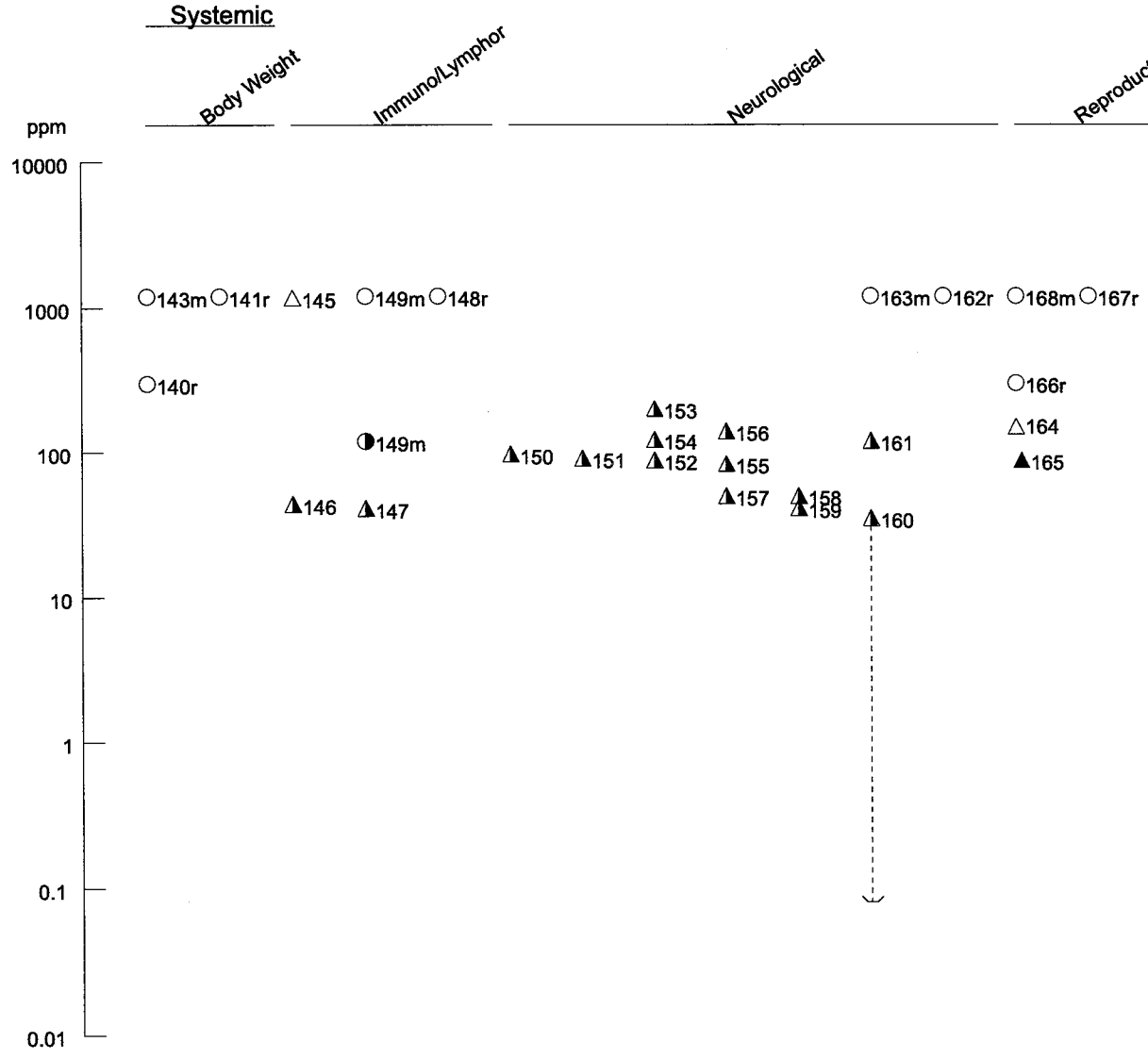


Figure 2-1. Levels of Significant Exposure to Toluene - Inhalation (continued)

Chronic (≥365 days)



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

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

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

■ LD50/LC50
Minimal Risk for effects other than Cancer

more than 18 months had normal chest roentgenograms and did not report breathing difficulty (Guzelian et al. 1988).

Ten paint-sprayers exposed to 13 detected solvents (primarily 0.8–4.8 ppm toluene and isobutylacetate) and dusts had morphological changes in the nasal mucosa (Hellquist et al. 1983). However, there was no conclusive association between duration of exposure and mucosal abnormalities. Forty-two workers exposed to mixtures of solvents, of which toluene was generally a major component, reported symptoms of nasal irritation, in addition to eye irritation, nausea, skin conditions, dizziness, and headaches (Winchester and Madjar 1986). The concentrations of toluene to which the workers were exposed ranged from 1 to 80 ppm (mean of 15 ppm). However, concurrent exposure to a mixture of solvents and dusts in these studies precludes establishing an unequivocal causal relationship between exposure to toluene and mucosal irritation.

Rats exposed to 30 or 300 ppm toluene 6 hours/day, 5 days/week for 4 weeks showed histopathological changes in the tracheal epithelium (Poon et al. 1994). Rats exposed to 600 ppm for 5 weeks, 7 hours/day showed irritation of the lung and rats exposed to 2,500 and 5,000 ppm had pulmonary lesions (von Oettingen et al. 1942). No signs of respiratory distress or histological abnormalities were observed in the lungs of mice exposed to 4,000 ppm 3 hours/day, for 8 weeks, or in rats and mice exposed to12,000 ppm for seven 10-minute periods per day separated by a 20-minute recovery period (Bruckner and Peterson 1981b). However, this study did not include a histological examination of the upper respiratory tract and may therefore not have observed damage to this region. Alternatively, the different results reported by von Oettingen et al. (1942) and Bruckner and Peterson (1981b) may be explained by differences in the daily exposure duration with the shorter duration causing the less severe effects.

Significantly increased relative lung weights were reported in rats and male mice exposed to 2,500 and 3,000 ppm (6.5 hours/day, 5 days/week for 14–15 weeks) and in female mice exposed to >100 ppm toluene (NTP 1990). Mild-to-moderate degeneration of the olfactory and respiratory epithelium were observed in rats exposed to 600 ppm or 1,200 ppm 6.5 hours/day, 5 days/week for 15 months (NTP 1990). Minimal hyperplasia of the bronchial epithelium was seen in 4/10 mice exposed to 1,200 ppm, but no other treatment-related damage to the respiratory tract was observed (NTP 1990).

Inflammation of the nasal mucosa, erosion and metaplasia of the olfactory epithelium, and degeneration of the respiratory epithelium were reported in rats exposed to 600 or 1,200 ppm for 2 years (6.5 hours/day, 5 days/week) (NTP 1990). These effects were not observed in mice exposed to the same

concentrations for 2 years. No histopathological lesions were observed in the upper respiratory tract or lungs of rats exposed for 2 years to 300 ppm toluene (CIIT 1980).

Cardiovascular Effects. Cardiac arrhythmia is a cause of death that has been associated with some solvent abuse fatalities. However, studies in laboratory animals do not provide convincing support for a direct effect of toluene on the cardiovascular system (Bruckner and Peterson 1981b; CIIT 1980; NTP 1990). One study of acute exposure to a lethal concentration of toluene reported the induction of arrhythmia, but the authors suggest that this was due to a predisposing arrhythmia-producing heart abnormality (Ikeda et al. 1990). Other studies of acute exposure to near-lethal concentrations have reported a non significant increase in heart rate (Vidrio et al. 1986) or a reduction of experimentally-induced arrhythmia (Magos et al. 1990). Chronic exposure to toluene concentrations up to 1,200 ppm did not induce cardiovascular system lesions in two well-conducted animal studies (CIIT 1980; NTP 1990) and did not appear to be directly toxic to the cardiovascular system.

Cardiac arrhythmias were noted in two adult males who were found semi-conscious after suffering from toluene intoxication (>7,000 mg/m^3 toluene, 1,862 ppm) while removing glue from tiles in a swimming pool (Meulenbelt et al. 1990). Response seemed to be variable between these individuals. One man was exposed for 2 hours and exhibited a rapid heartbeat (sinus tachycardia), while the second man, exposed for 3 hours, exhibited a slow heartbeat (bradycardia) (Meulenbelt et al. 1990). Severe sinus bradycardia was also reported in a comatose man with severe toluene intoxication who had sniffed approximately 250 mL of thinner containing more than 50% toluene (Einav et al. 1997). No effects on systolic or diastolic blood pressure or pulse rate were reported in volunteers exposed to 800 ppm toluene for 3 hours (von Oettingen et al. 1942).

Cardiovascular response was assessed in 25 dogs killed by rebreathing 1 L of air containing 30,000 ppm toluene via an endotracheal tube (Ikeda et al. 1990). In most cases, death was due to hypoxia, but four of the dogs developed transient arrhythmia and in one case, death was due to ventricular fibrillation. The authors suggested that toluene had a direct effect on the septal and ventricular muscles of the heart, which permitted the development of fatal arrhythmias in sensitive dogs (Ikeda et al. 1990). Inhalation by anesthetized rats of 66,276 ppm toluene for 30 minutes (35 minutes inhalation of this concentration was fatal) produced a non significant increase in heart rate and changes in electrocardiographs indicative of depressed ventricular conduction (Vidrio et al. 1986). However, in rats with arrhythmias induced by aconitine injection or coronary ligation, a 15-minute exposure to 6,867 ppm toluene, 10 minutes before aconitine treatment significantly reduced the number of ventricular ectopic beats (Magos et al. 1990).

No histological abnormalities were observed in the hearts of mice exposed to 4,000 ppm for 3 hours/day, for 8 weeks or to mice and rats exposed to 12,000 ppm for 70 minutes/day for 8 weeks (Bruckner and Peterson 1981b). There were also no histopathological lesions of the heart that could be attributed to toluene in rats exposed to 300 ppm for 24 months (6 hours/day) (CIIT 1980) or in rats and mice exposed to up to 1,200 ppm for 24 months (6.5 hours/day) (NTP 1990). However, there were increased heart weights in rats and female mice exposed to 2,500 ppm toluene for 14–15 weeks (6.5 hours/day) (NTP 1990).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to toluene.

The incidence of ulcers of the forestomach was marginally, but not significantly, increased in male rats exposed to concentrations of 600–1,200 ppm toluene for 2 years (NTP 1990). These effects were not reported in mice or female rats exposed under the same conditions. There were no gastrointestinal effects in rats and mice exposed to up to 2,500–3,000 ppm toluene for 14–15 weeks(NTP 1990).

Hematological Effects. Hematological effects were not reported after inhalation exposure to toluene in the majority of recent human and animal studies. However, before the mid-1950s, chronic occupational exposure to toluene was associated with hematological effects in the same studies (Greenburg et al. 1942; Wilson 1943). These effects are now attributed to concurrent exposure to benzene, a common contaminant of toluene at that time (EPA 1985c). More recent studies of workers exposed to toluene or to mixed solvents containing toluene have not found consistent evidence for abnormal hematological parameters(Banfer 1961; Matsushita et al. 1975; Tahti et al. 1981; Ukai et al. 1993; Yin et al. 1987). Decreased leukocyte counts were observed in some animal studies (Hobara et al. 1984a; Horiguchi and Inoue 1977; NTP 1990; von Oettingen et al. 1942), but not in others (Ono et al. 1996; Poon et al. 1994). There is evidence, however, that the decrease is a reversible phenomenon (von Oettingen et al. 1942). The toxicological significance of transitory decreases in leukocyte counts is not clear. It appears that toluene affects the blood, but blood is probably not a critical target tissue following toluene exposure.

No effects on leukocyte counts were observed in volunteers exposed to 800 ppm toluene for 3 hours (von Oettingen et al. 1942). Two workers accidentally exposed to about 1,862 ppm for three hours had normal values for hematological and blood chemistry variables with the exception of an elevated union gap (Meulenbelt et al. 1990).

Ukai et al. (1993) reported no hematologic effects in 452 toluene-exposed shoemakers and printers (average exposure of 24.7 ppm) compared with unexposed controls from the same factories. Exposure was estimated from personal monitoring data, and at least 90% of total solvent exposure was due to toluene. Workers involved in printing, shoemaking, and audio equipment production, and exposed to 41 ppm toluene had significantly decreased lymphocyte counts when compared to controls (Yin et al. 1987). However, total leukocyte counts were not different from controls since the decrease in lymphocytes was counterbalanced by an increase in eosinophils. No significant hematological effects were observed in workers engaged in shoe-making (Matsushita et al. 1975) or printing (Banfer 1961) who were exposed to toluene for several years. The studies were limited by small cohort size and a lack of historical exposure data. Workers were exposed to atmospheric concentrations of toluene up to 600 ppm, but individual exposure monitoring was generally not performed. As a result, the studies had only limited power to detect adverse hematological effects in toluene-exposed workers.

In contrast, workers exposed for several years to toluene (benzene concentration <0.01%) in a tarpaulin factory had increased blood leukocyte counts (Tahti et al. 1981). Toluene exposure concentrations, which ranged from 20 to 200 ppm were similar to those reported by Banfer (1961). However, this study is limited by small cohort size, a lack of historical exposure monitoring, and the probability that workers were exposed to mixtures of chemicals.

Results of animal studies support the observation of decreased leukocyte counts following exposure to toluene. Decreased leukocyte counts were observed in dogs exposed acutely to 500 ppm of toluene (Hobara et al. 1984a). Throughout a 20-day exposure to 10, 100, and 1,000 ppm of toluene, mice exhibited a concentration-related decrease in thrombocyte counts (Horiguchi and Inoue 1977). The 100 and 1,000 ppm groups were reported to have decreased erythrocyte counts; but the authors did not provide analysis of the results or discuss the findings further. Both studies are limited by small numbers of animals in the treatment groups. Slight hypoplasia of the bone marrow was observed in mice exposed to 1,000 ppm (Horiguchi and Inoue 1977), but the effect was not statistically significant and was not found in mice or rats exposed to up to 1,200 ppm for 2 years (NTP 1990). Rats exposed to 2,500 and 5,000 ppm of toluene for 5 weeks had a daily, temporary decrease in leukocyte counts, but counts had normalized by the next day (von Oettingen et al. 1942). Decreased leukocyte counts were also reported in female rats exposed to 1,250 ppm toluene for 15 weeks, but not in mice or male rats exposed to up to 2,500 ppm (NTP 1990).

Increased hematocrit and blood glucose levels were observed in male rats exposed to 2,000 ppm toluene for 48 hours (Tahti et al. 1983). Erythrocyte membranes were stronger and less susceptible to lysis in rats exposed to 2,000 ppm of toluene than in controls (Korpela et al. 1983). This was demonstrated to be a reversible phenomenon since membrane strength returned to normal after toluene had dissipated from the system (Korpela and Tahti 1984). Other lipophilic agents such as anesthetics, tranquilizers, narcotics, and steroids have a similar effect on membrane strength (Magos et al. 1990).

No significant changes in hematological variables were observed in male rats exposed to 2,000 ppm 6 hours/day for 90 days (Ono et al. 1996), or in rats exposed to 300 ppm 6 hours/day, 5 days/week for 4 weeks (Poon et al. 1994).

In one chronic study, rats exposed to 100 or 300 ppm of toluene had significantly reduced hematocrit levels (CIIT 1980). However, in another study, no consistent effects on hematological variables were reported for mice or rats exposed to toluene at levels up to 1,200 ppm for 2 years (NTP 1990).

Musculoskeletal Effects. A 29-year-old man who had been sniffing glue containing toluene (concentration not specified) for 18 years and complained of severe muscle weakness was diagnosed with rhabdomyolysis (an acute disease of the skeletal muscles evidenced by myoglobin in the blood and urine) (Hong et al. 1996).

No histological effects on bone were reported in mice or rats exposed to toluene at concentrations up to 1,200 ppm for 2 years (NTP 1990).

Hepatic Effects. Studies of chronic toluene abusers or occupationally-exposed humans, have provided little evidence for serious liver damage due to inhaled toluene. Some studies of workers who were occupationally exposed to average concentrations between about 30 and 350 ppm toluene reported liver effects such as increased serum levels of enzymes (Guzelian et al. 1988; Svensson et al. 1992b), but others recorded no adverse effects (Lundberg and Hakansson 1985; Seijii et al. 1987; Ukai et al. 1993). A number of animal studies have reported increased liver sizes or minor ultrastructural changes in rats exposed to concentrations of toluene ranging from 150 ppm for 30 days to 4,000 ppm 3 hours/day for 8 weeks (Bruckner and Peterson 1981b; Kjellstrand et al. 1985; NTP 1990), but other studies have recorded no adverse effects in rats and mice exposed to concentrations of up to 1,200 ppm for 2 years (CIIT 1980; Kyrklund et al. 1987; NTP 1990).

No effects on blood levels of bilirubin, alkaline phosphatase activity, serum aspartate aminotransferase activity or serum alanine aminotransferase activity were reported for two workers accidentally exposed to 1,862 ppm toluene for three hours (Meulenbelt et al. 1990). Eight men from a printing factory employing 289 workers exposed to toluene at concentrations of less than 200 ppm, exceeded the upper end of the normal range for blood levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (AP) and had an ALT/AST ratio greater than 1 (Guzelian et al. 1988). Liver biopsies showed centrilobular and periportal fat accumulation and Kupffer cell hyperplasia. None of the men reported drinking alcohol to excess, but they may have had minimal occupational exposure to methyl alcohol, ethyl alcohol, diethyl ether, trichloroethylene, and lacquer thinners which could have confounded the results.

An early study of 106 painters exposed to toluene in an airplane factory reported enlargement of the liver in 30.2% of the exposed men, versus 7% of the control group (Greenburg et al. 1942). However, before the mid-1950s, chronic occupational exposure to toluene was associated with exposure to benzene, a common contaminant of toluene at that time (EPA 1985c), and this is a confounding factor for this study. Serum alkaline phosphatase values were significantly greater than controls in a group of 47 rotogravure workers occupationally exposed to a time-weighted-average (TWA) toluene concentration of 11–47 ppm (midpoint 29 ppm) for 3–39 years than in controls (Svensson et al. 1992b). The difference in alkaline phosphatase values remained significant even when the data were corrected to eliminate nine workers who reported consumption of alcoholic beverages.

In contrast, no significant elevations in serum liver enzymes were found in another group of 452 shoemakers and printers (exposed to average concentrations of 24.7 ppm toluene) compared with unexposed workers from the same factories (Ukai et al. 1993). Women working in a shoe factory for an average of more than 3 years and exposed to toluene concentrations which varied from 65 ppm (15-100 ppm) in winter and 100 ppm (10-200 ppm) in summer showed no changes in several serum variables indicative of liver damage compared with a control group of unexposed workers from the same factory (Matsushita et al. 1975).

A group of 157 female shoemakers exposed for 2–14 months to toluene (7–324 ppm) had decreased serum levels of lactate-dehydrogenase (LDH) as compared to controls, but levels of 8 other serum enzymes monitored as indices of liver damage were normal (Seiji et al. 1987). These workers were also exposed to *n*-hexane, cyclohexane, and methyl ethyl ketone at concentrations generally 1/10th of the toluene concentration. Because LDH is present in almost all body tissues, this finding cannot be

attributed to an effect in the liver with any certainty. A group of 47 Swedish paint industry workers exposed for more than 10 years to mixed organic solvents (xylene, toluene, isobutanol, n-butanol, ethanol, ethylacetate, n-butylacetate, mineral spirits, methylacetate, methylene chloride, methyl ethyl ketone, and isopropanol) did not have elevated serum concentrations of liver enzymes when compared to nonexposed controls (Lundberg and Hakansson 1985). Each of these studies is limited by small cohort size, exposure to multiple solvents, and by a lack of historical exposure monitoring data. As a result, the studies had only limited power to detect adverse effects caused by toluene.

Several case studies have reported effects on the liver from toluene exposure. Acute fatty liver during pregnancy was reported in a 26-year-old woman exposed for at least 2 months to toluene in glue. A liver biopsy done 9 days postpartum showed cytoplasmic change in the hepatocytes; however, there was no clinical or biochemical evidence of liver disease 1 month later (Paraf et al. 1993). A painter who had been exposed to toluene for 5 years exhibited hepatotoxicity, with fatty degeneration of hepatocytes and infiltration by lymphocytes (Shiomi et al. 1993).

Acute exposure to toluene has been reported to produce biochemical and ultrastructural changes in the livers of experimental animals. Mice, rats, and rabbits exposed to 795 ppm of toluene for 7 days showed increased liver weights and cytochrome P450 levels compared to unexposed controls (Ungvary et al. 1982). Electron microscopy revealed ultrastructural changes (increased rough or smooth endoplasmic reticulum) in the livers of all three species (Ungvary et al. 1982). Cytochrome b_5 levels were also increased in exposed rats and rabbits but were not measured in mice (Ungvary et al. 1982). Male rats exposed to 2,000 ppm toluene for 48 hours had increased serum levels of alanine aminotransferase and aspartate aminotransferase (Tahti et al. 1983). Exposure of rats to 4,000 ppm toluene for 6 hours resulted in a significant increases in hepatic levels of cytochrome P450 (CYP) 2E1, increased hepatic activities of nitrosodimethylamine demethylase and 7-pentoxyresorufin O-dependentylase and decreased levels of CYP2C11 (Wang et al. 1996).

Intermediate exposure of animals to toluene has generally produced liver responses similar to those reported for acute exposure. Increased liver weights were reported for male mice exposed to12,000 ppm toluene, 3 hours/day, 5 days/week for 8 weeks (Bruckner and Peterson 1981b), female mice exposed to 150 ppm continuously for 30 days (Kjellstrand et al. 1985), rats exposed to $1,200 ppm (males) or $2,500 ppm (females), or mice exposed to $625 ppm for 14 or 15 weeks (NTP 1990). However, male rats and mice exposed to 12,000 ppm toluene for 8 weeks (seven 10-minute exposures separated by 20-minute recovery periods) had decreased liver weights (Bruckner and Peterson 1981b), and no change

in liver weight was observed in rats exposed to 320 ppm (Kyrklund et al. 1987), male mice exposed to 150 ppm (Kjellstrand et al. 1985) continuously for 30 days, or rats exposed to 30 or 300 ppm toluene 6 hours/day, 5 days/week for 4 weeks (Poon et al. 1994). No effect on the liver was reported for rats exposed to 200–5,000 ppm toluene for 7 hours/day for 5 weeks (Von Oettingen et al. 1942).

Alkaline phosphatase activity was significantly elevated in male rats exposed to 300 ppm for 6 hours/day, 5 days/week for 4 weeks (Poon et al. 1994) and centrilobular hepatocellular hypertrophy was noted in male mice exposed to 2,500–3,000 ppm toluene for 14 weeks (NTP 1990).

No significant gross or histpathological liver changes or liver weight changes were found in rats exposed to toluene at 300 ppm (CIIT 1980) or rats or mice exposed to up to 1,200 ppm 6–6.5 hours/day, 5 days/week for up to 2 years (NTP 1990).

Renal Effects. Studies of chronic toluene abusers, occupationally exposed workers, and laboratory animals have provided little support for serious kidney damage due to inhaled toluene. Chronic abuse of toluene can produce acidosis, but in most cases, renal dysfunction is transient and normal function returns when exposure ceases (Goodwin 1988; Kamijo et al. 1998; Meulenbelt et al. 1990; Patel and Benjamin 1986). In general, studies of workers occupationally exposed to 100–200 ppm toluene, which assessed changes in tests of kidney function, have not shown significant effects (Askergren et al. 1981a; Nielsen et al. 1985; Stengel et al. 1998). Animal studies indicate that inhalation of toluene causes concentration-dependent kidney damage in rats, but only after chronic exposure to concentrations $600 ppm for at least 6 hours/day (Bruckner and Peterson 1981b; CIIT 1980; NTP 1990; Ono et al. 1996; Poon et al. 1994).

Several cases have been reported where occupational exposure to toluene or toluene abuse was associated with acidosis (Gerkin and LoVecchio 1998; Goodwin 1988; Jone and Wu 1988; Meulenbelt et al. 1990; Patel and Benjamin 1986). Acidosis generally reflects the inability of the kidneys to maintain the pH balance of the blood either due to saturation of kidney transport of hydrogen ion or a defect in tubular function. Severe renal tubular acidosis was observed in five pregnant women who were chronic abusers of paints containing toluene (Goodwin 1988). When paint-sniffing ended, normal acid-base balance returned within 72 hours, indicating that permanent damage to the tubules had not occurred. However, one 19-year-old male chronic solvent abuser was found, through a renal biopsy, to have severe tubular interstitial nephritis and focal tubular necrosis indicative of prolonged irritation of the kidney (Taverner et al. 1988). This patient required hemodialysis to correct hematuria and oliguria which was present at the time of his hospital admission. Hemodialysis was also required for a 22-year-old male chronic

solvent abuser with acidosis and hypokalemia (Gerkin and LoVecchio 1998). A 22-year-old woman, who had sniffed approximately 6 L of toluene during the previous month, was found to have metabolic acidosis and histological evidence of tubular injury. The acidosis normalized, but both proximal and distal tubular dysfunction persisted (Kamijima et al. 1994). Proteinuria, hematuria, and urinary calculi were reported in three solvent abuse case studies (Kaneko et al. 1992); the abused product was primarily toluene in one case. Autopsy of a 19-year-old woman, who had sniffed thinner containing 67% toluene for 5 years, revealed severe renal tubular degeneration and necrosis (Kamijo et al. 1998).

A group of 43 printing trade workers exposed to inks containing toluene, alcohols, and ethyl acetate for 9–25 years were experimentally exposed to 382 mg/m^3 (102 ppm) of toluene for 6.5 hours (Nielsen et al. 1985). No significant differences in excretion of albumin and β-2-microglobulin were observed either before or after exposure when the workers were compared to controls matched by age, educational level, and smoking habits (Nielsen et al. 1985).

In a longitudinal study of 92 printers exposed to 97–232 mg/m^3 (26–62 ppm) toluene, markers of early renal damage (microalbumin, N-acetyl-b-D-glucosaminidase, and alanine-aminopeptidase) were not significantly elevated in urine, but creatinine clearance was higher among exposed workers than unexposed controls (Stengel et al. 1998). Comparison of a group of 42 printers, occupationally exposed to 300–400 mg/m^3 toluene (80–107 ppm), with a group of age-matched, unexposed controls showed that printers excreted significantly more albumin than controls, but no increase in the excretion of β-2-microglobulin was observed (Askergren et al. 1981a). Glomerular filtration rate in a group of 34 printers (toluene exposure level not stated) was slightly increased compared with unexposed controls, but the difference was not significant (Askergren et al. 1981b).

In an early animal study, toluene produced pathological changes in the kidneys of rats. Inhalation of 600–5,000 ppm of toluene 7 hours per day for 5 weeks caused the formation of renal casts within the collecting tubules of exposed rats (von Oettingen et al. 1942). In a recent study (Ono et al. 1996), an increase in kidney weights and necrosis of kidney tubules were seen in male rats exposed to 2,000 ppm toluene for 90 days. No histological abnormalities were observed in the kidneys of mice exposed to 4,000 ppm for daily 3-hour periods or mice and rats exposed to 12,000 ppm for 70 minutes/day, 5 days/week for 8 weeks, but kidney weights were significantly decreased in rats and mice exposed to 12,000 ppm (Bruckner and Peterson 1981b). Increased relative kidney weights, but no histological lesions were seen in rats exposed for 15 weeks and female mice exposed to toluene for 14 weeks at

1,250 ppm (6.5 hours per day) (NTP 1990). No effects on the kidneys were observed in rats exposed to 30 or 300 ppm toluene for 4 weeks (Poon et al. 1994).

Gross and microscopic pathological examination of rats chronically exposed to 300 ppm of toluene for 24 months found no treatment-related renal effects (CIIT 1980). Nephropathy was observed in most (96–98%) of the rats (including controls) from a 2-year inhalation study; the severity increased with concentration (600–1,200 ppm) (NTP 1990). The incidence of renal tubular cysts increased with concentration level in males. No renal lesions were reported in mice exposed under the same conditions (NTP 1990). Since the only essential difference between the CIIT and NTP studies was the concentration level used, it appears that the occurrence of renal tubular cysts was concentration-related.

Endocrine Effects. A 29-year-old man who had been sniffing glue containing toluene (concentration not specified) for 18 years was diagnosed with hypothyroidism (Hong et al. 1996). Autopsy of a 19-year-old woman who had been sniffing thinner (67% toluene) for 5 years revealed histological evidence of massive bilateral adrenal hemorrhage with severe degeneration and necrosis of the adrenal cortex (Kamijo et al. 1998). Plasma levels of follicle stimulating hormone, lutenizing hormone, and testosterone were reduced in printers exposed to median toluene levels of 36 ppm for an average of 25 years compared with unexposed controls (Svensson et al. 1992a).

Female rats exposed to 30 or 300 ppm toluene for 6 hours/day, 5 days/week for 4 weeks showed a treatment-related reduction in follicle size of the thyroid (Poon et al. 1994). No effect on the adrenal glands was reported for rats exposed to 200–5,000 ppm toluene for 7 hours/day for 5 weeks (Von Oettingen et al. 1942). No gross morphological abnormalities on the pancreas, adrenal, or thyroid glands were observed in rats exposed to 100–2,000 ppm toluene for 95 days (API 1985). Mice exposed to up to 2,500 ppm for 14 weeks (NTP 1990), rats exposed to up to 3,000 ppm for 15 weeks, and mice and rats exposed to up to 1,200 ppm for 2 years (NTP 1990) showed no histological abnormalities in the pancreas, adrenal, or thyroid glands.

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to toluene.

No effects on the skin were observed in rats exposed to 100–2,000 ppm toluene for 95 days (API 1985).

Ocular Effects. Humans exposed for 6–8 hours to toluene concentrations of 100 ppm and greater developed irritation of the eyes (Andersen et al. 1983; Baelum et al. 1985; Carpenter et al. 1944; Meulenbelt et al. 1990). No irritation was reported with 6 hours of exposure to 40 ppm toluene (Andersen et al. 1983). Reports of color vision deficits in occupationally exposed workers have linked increased color confusion with chronic exposure to <100 ppm toluene (Zavalic et al. 1998a, 1998b, 1998c). These studies are discussed in the Section 2.2.1.4, Neurological Effects.

Pregnant rats exposed to 2,000 ppm 6 hours/day for 21 days showed lacrimation (Ono et al. 1996), but no lacrimation or discharge was reported for male, female, or pregnant female rats exposed to 100–2,000 ppm, 6 hours/day for 95 days (API 1985).

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

Body weights in rats decreased compared with controls following inhalation exposure to toluene concentrations of 2,000 ppm for 48 hours (Tahti et al. 1983), 2,000 ppm, 8 hours/day, 7 days/week for 11 weeks (Pryor 1991), 320 ppm, 24 hours/day for 30 days (Kyrklund et al. 1987), 8,000 ppm 2–2.5 hours/day, 5 days/week for 13 weeks (Mattsson et al. 1990), 12,000 ppm 70 minutes/day, 5 days/week for 8 weeks (Bruckner and Peterson 1981b), 2,500 ppm, or 6.5 hours/day for 15 weeks (NTP 1990). In contrast, no effects on body weights were observed in rats or mice exposed to 1,000 ppm toluene for 6 hours/day, 5 days/week, for 20 or 42 days (API 1997; Horiguchi and Inoue 1977), in rats exposed to up to 2,000 ppm toluene 6 hours/day for 90 or 95 days (API 1985; Ono et al. 1996), or in rats or mice exposed to up to 1,200 ppm toluene 6–6.5 hours/day for 2 years (CIIT 1980; NTP 1990). Decreased body weights were seen in female and male mice exposed 6.5 hours/day to concentrations $100 and 2,500 ppm, respectively (NTP 1990), and in male mice exposed to 4,000 ppm, 3 hours/day or 12,000 ppm 70 minutes/day for 8 weeks (Bruckner and Peterson 1981b).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to toluene.

2.2.1.3 Immunological and Lymphoreticular Effects

Only limited data are available on the immunological or lymphoreticular effects of inhalation exposure to toluene. Studies in exposed workers are confounded to varying degrees by exposure to multiple solvents,

but indicate that there may be slight effects of toluene on immunoglobins, leukocytes, and lymphocytes, but the significance of these effects in humans is uncertain. A single mouse study reported that exposure to concentrations >100 ppm, 3 hours/day for 4 weeks decreased resistance to respiratory infection (Aranyi et al. 1985).

No differences in serum IgG, IgA and IgM values were noted when rotogravure printers exposed to concentrations of 104–1,170 ppm for an average of 13 years were compared to office workers at the same facility (Pelclova et al. 1990). Blood IgE levels in 92 printers exposed to 97–232 mg/m^3 (26–62 ppm) toluene for an average of 16 years were significantly elevated compared to unexposed controls, and a dose-response relation was observed between cumulative toluene exposure and IgE levels (Stengel et al. 1998). Total lymphocytes were significantly decreased in workers involved in shoemaking, printing, and audio equipment production (Yin et al. 1987). Mean toluene exposures were 41 ppm for females and 46 ppm for males over an average of 82 months.

A decrease in the T lymphocyte count of workers occupationally exposed to a mixture of benzene (0–116 ppm), toluene (0–160 ppm), and xylene (0–85 ppm) was observed (Moszczynsky and Lisiewicz 1984). However, no signs of diminished immunological function or disturbances in immune skin reactions against such antigens as tuberculin or distreptase were observed in the subjects studied. The reduction of T lymphocytes may have been the result of the depressive effect of benzene on the lymphocyte system. Workers exposed to a mixture of 0.8–40 ppm toluene (0.003–0.16 mg/L), 56–940 ppm benzene (0.18–3.0 mg/L), and 40–609 ppm xylene (0.18–3.0 mg/L) had significantly lower serum IgG and IgA levels than unexposed controls (Lange et al. 1973). Leukocyte agglutinins for autologous leukocytes and increased leukoagglutination titer in human sera after incubation with the solvents were also observed (Lange et al. 1973). The results of these studies are confounded by mixed exposure and their significance is therefore uncertain.

A single 3-hour exposure of mice to 2.5–500 ppm toluene produced a significant increase in susceptibility to respiratory infections compared to unexposed controls when mice were challenged by *Streptococcus zooepidemicus* (Aranyi et al. 1985). Exposure to 1 ppm for 3 hours, 5 days (3 hours/day), or 4 weeks (3 hours/day) produced no significant difference in susceptibility compared to controls. Pulmonary bactericidal activity was decreased at concentrations of 2.5 ppm and 100–500 ppm, but not at concentrations of 5–50 ppm. The bactericidal activity of the lung was decreased during the 5-day treatment but not with the 4-week treatment. The authors hypothesized that toluene exerted an adverse effect on alveolar macrophage function, thereby decreasing disease resistance.

No changes in weight or histology of the spleen were recorded for rats exposed to 30–5,000 ppm toluene, 6–7 hours/day for 4–5 weeks (Poon et al. 1994; von Oettingen et al. 1942), or for the spleen or thymus of rats and mice exposed to toluene concentrations up to 3,000 ppm for 14–15 weeks (NTP 1990). Exposure of mice and rats to up to 1,200 ppm, 6.5 hours/day for 2 years produced no histological changes in the thymus, but there was an increased incidence of pigmentation of the spleen in male mice exposed to concentrations $120 ppm (NTP 1990).

Decreased thymus weights were observed in male rats exposed to 2,000 ppm 6 hours/day for 90 days (Ono et al. 1996) and in dams exposed to 600 ppm 6 hours/day during gestation days 7–17 (Ono et al. 1995). However, no effects on the thymus were reported in rats and mice exposed 6 hours/day to up to 1,200 ppm for 2 years or up to 3,000 ppm toluene for 14–15 weeks (NTP 1990) or in male rats exposed to 1,000 ppm toluene for 6 hours/day for up to 42 days (API 1997).

The highest NOAEL values and all LOAEL values for each reliable study for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Dysfunction of the central nervous system is a critical human health concern following acute, intermediate, or chronic inhalation exposure to toluene. Chronic toluene abuse in humans has been associated with neurotoxic symptoms, narcosis, and death (Byrne et al. 1991; Caldemeyer et al. 1996; Devathasan et al. 1984). Case reports from chronic abusers indicate that prolonged exposure to toluene results in permanent damage to the central nervous system (Byrne et al. 1991; King et al. 1981; Rosenberg et al. 1988b). Neurotoxic symptoms and reduced ability in tests of cognitive and neuromuscular function have been observed in humans occupationally exposed to average concentrations as low as 80–150 ppm (Boey et al. 1997; Murata et al. 1993; Orbaek and Nise 1989; Vrca et al. 1995, 1997b; Yin et al. 1987). Performance deficits in tests of neurobehavior have also been observed in volunteers acutely exposed to controlled concentrations >50 ppm (Andersen et al. 1983; Baelum et al. 1985; Echeverria et al. 1991; EPA 1985c; Iregren 1986; Rahill et al. 1996; von Oettingen et al. 1942) and in laboratory animals repeatedly exposed to >500 ppm toluene (Larsby et al. 1986; Lorenzana-Jimenez and Salas 1990; Miyagawa et al. 1998; Pryor 1991). Studies of occupationally exposed workers also indicate that chronic exposure to average concentrations as low as 30–130 ppm damages hearing and color vision presumably involving, at least in part, effects on neurological components of these systems (Abbate et al. 1993; Morata et al. 1997; Zavalic et al. 1998a, 1988b, 1988c). Hearing loss has also been

reported in laboratory animals exposed to 700–1,500 ppm toluene (Campo et al. 1997; Johnson and Canlon 1994; Lataye and Campo 1997; Pryor et al. 1984b).

Experimental studies in volunteers show that acute exposure to toluene concentrations below 50 ppm results in few, if any, observable effects, but signs of neurological impairment have been observed with acute exposure to concentrations greater than 50 ppm. For example, exposure to 40 ppm of toluene for 6 hours did not produce statistically significant differences in the results of tests measuring psychometric performance and subjective evaluations of well being when compared to controls (Andersen et al. 1983). In contrast, 6–6.5-hour exposures to 100 ppm toluene caused fatigue, sleepiness, headaches, nausea, decreased manual dexterity, decreased color discrimination, decreased accuracy in visual perception, and decreased accuracy in multiplication tests (Andersen et al. 1983; Baelum et al. 1985). An acute inhalation MRL of 1 ppm was calculated as described in the footnote in Table 2-1 and Appendix A, based on the NOAEL (40 ppm) from the study by Andersen et al. (1983).

Several other human studies support the derivation of the acute inhalation MRL and the hypothesis that subtle neurological effects can occur with acute exposure to concentrations in the 75–150 ppm range. Exposure of volunteers to 0, 75, or 150 ppm toluene for 7 hours caused a concentration-related impairment of function on digit span, pattern recognition, the one-hole test, and pattern memory (Echeverria et al. 1991). There was an effect on the results of the symbol digit test, but the effect was not concentration-related. Tests were administered to each subject before exposure and at the end of the exposure period. The treatment effect between groups was smaller than the variation of subjects within the group, thus each subject was used as their own control to more accurately assess the changes in performance due to exposure. There were no differences in the results on simple reaction time, mood (profile on mood scale), visual memory, hand-eye coordination, verbal short-term memory (Sternberg test), finger tapping, reaction time, continuous performance test, and critical tracking test. Six volunteers exposed to 100 ppm toluene for 6 hours, followed by exercise, showed significantly lower results on neuropsychological tests than volunteers exposed to clean air only (Rahill et al. 1996). Exposure of 26 painters to controlled amounts of toluene (5 or 80 ppm) for 4 hours did not change their performance in tests of reaction time, color-word vigilance, or memory reproduction (Iregren 1986). Workers in a printing factory (exposed to <200 ppm toluene) returning to work after a 4-day vacation reported a feeling of mild intoxication to which they became tolerant within 1 or 2 days (Guzelian et al. 1988). At concentrations of 200–800 ppm, acute exposures initially resulted in excitatory effects such as exhilaration and lightheadedness. These effects were followed by the development of narcosis,

characterized by impaired intellectual, psychomotor, and neuromuscular effects with increased duration of exposure (EPA 1985c; von Oettingen et al. 1942).

Humans exposed to high levels of toluene as a result of solvent abuse or industrial accidents have displayed serious central nervous system dysfunction. Accurate exposure data are not available for these individuals, but the concentrations inhaled by chronic abusers have been estimated to range from 4,000 to 12,000 ppm (Gospe et al. 1994). In some cases, the degree of central nervous system depression was sufficient to result in death. Prolonged abuse has been reported to cause permanent damage resulting in abnormal electroencephalogram (EEG) activity, ataxia, tremors, temporal lobe epilepsy, paranoid psychosis, hallucinations, nystagmus (involuntary eye movement), cerebral atrophy, and impaired speech, hearing, and vision (Byrne et al. 1991; Devathasan et al. 1984; Hunnewell and Miller 1998; King et al. 1981; Maas et al. 1991; Meulenbelt et al. 1990; Miyagi et al. 1999; Ryu et al. 1998; Suzuki et al. 1983).

In two hospitalized patients with a history of solvent abuse, there was a decrease in intelligence quotient when the results of tests administered before solvent abuse began were compared to those measured during hospitalization for long-term abuse (Byrne et al. 1991). Examination of 19 children (ages 8–14 years) hospitalized with acute encephalopathy due to toluene exposure indicated that 5 of the children retained psychological impairment and personality change when discharged from the hospital, while one child had a persistent cerebellar ataxia 1 year after cessation of toluene abuse (King et al. 1981).

In general, results from case studies of toluene abusers suggest that some of the neurological symptoms associated with chronic toluene abuse may be the result of permanent structural changes in the brain. Evaluation of chronic toluene abusers by magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) has shown an increase in the white matter signal, a loss of gray and white matter differentiation, and decreased perfusion in the cerebral cortex, basal ganglia, and thalami (Caldemeyer et al. 1996; Filley et al. 1990; Ikeda and Tsukagoshi 1990; Kamran and Bakshi 1998; Rosenberg et al. 1988a; Ryu et al. 1998; Yamanouchi et al. 1995). Cerebral, cerebellar, and brainstem atrophy were also present (Kamran and Bakshi 1998; Rosenberg et al. 1988b). Correlations between clinical signs of neurological impairment and damage visible in MRI images have also been reported (Caldemeyer et al. 1996; Hormes et al. 1986; Rosenberg et al. 1988b). Abnormalities in MRI and brainstem auditory evoked response (BAER) results were still present in chronic abusers who had refrained from toluene exposure for two to nine months (Rosenberg et al. 1988b).

Toluene had an effect on pattern-visual evoked potentials in 32 males and 2 females who abused thinner containing toluene for 5–10 years. Statistical differences between controls and toluene abusers were seen on latencies of waves P-100 and N-145 (Poblano et al. 1996).

Murata et al. (1993) compared cardiac autonomic function in printers exposed to 83 ppm airborne toluene for 1–36 years with matched controls. Autonomic function was evaluated from measurements of heart rate, the coefficient of variation in electrocardiographic R-R intervals, the distribution of nerve conduction velocities, and the maximal motor and sensory nerve conduction velocities in the median nerve. Some printers reported subjective symptoms such as fatigue, headache, and irritation. Heart rate was not significantly different in exposed individuals and controls. However, there were statistically significant reductions in electrocardiographic R-R intervals, indicating possible dysfunction of the autonomic nervous system. There was a significant decrease in the motor and sensory conduction velocity in the palm segment of the median nerve in toluene-exposed workers, but there was no significant difference in the distribution of the nerve conductance velocities between exposed and control subjects (Murata et al. 1993).

Several studies of workers repeatedly exposed predominantly to toluene in workplace air have found evidence for increased incidence of self-reported neurological symptoms (Orbaek and Nise 1989; Yin et al. 1987); performance deficits in neurobehavioral tests (Boey et al. 1997; Foo et al. 1990; Orbaek and Nise 1989); hearing loss (Abbate et al. 1993; Morata et al. 1997); changes in visual evoked potentials (Vrca et al. 1995, 1997a, 1997b), and color vision loss (Zavalic et al. 1998a, 1998b, 1998c).

A group of 95 workers exposed to TWA of 41–46 ppm toluene during shoemaking, printing, and audio equipment production were evaluated for symptoms and signs of exposure when compared to 130 control subjects (Yin et al. 1987). The incidence of health-related complaints among the toluene exposed workers was 2–3 times that of the controls. Dizziness was reported by about two-thirds of the toluene exposed respondents. These subjects also complained of headaches, sore throats, eye irritation, and difficulty with sleep. When the exposed subjects were divided into 2 groups, one with TWA exposures of less than 40 ppm and the other with exposures greater than or equal to 40 ppm, the incidence of headache and sore throat, but not dizziness, showed a concentration-response pattern (Yin et al. 1987). Tests of postural sway carried out on 27 United States Air Force workers exposed to jet fuel (mean cumulative exposure 23.8±6.1 ppm toluene) found a significant association between toluene exposure and increased postural sway (Smith et al. 1997). However, the results of this study are confounded by concurrent exposure to other chemicals, including benzene and xylene.

Thirty rotogravure printers from two plants and 72 unexposed workers completed a questionnaire designed to record their neurasthenic complaints and were given a series of tests designed to evaluate psychometric function (Orbaek and Nise 1989). At the time of the study (1985), 19 of the printers were exposed to TWA toluene levels of 11.6 ppm, and the remainder were exposed to 42.4 ppm. However, the printers had been exposed to solvents for at least 10 years (employment ranged 4–43 years), and estimated air concentrations at earlier times were much higher (as high as 453 ppm prior to 1970). Taking the midpoints in the ranges of concentration estimates for 1970–1985 for the two factories and calculating their mean yields, a representative exposure concentration of 140 ppm was determined. Significantly more printers reported neurasthenic symptoms than controls, but no significant differences were found between printers and controls for 10 of 11 psychometric tests and in the remaining test (Cylinder Board test of motor skill), printers performed better than controls.

A stronger correlation between impaired neurobehavioral performance and toluene exposure was seen in 30 female workers exposed to 88 ppm toluene as compared to 30 workers in the same facility exposed to only 13 ppm (Foo et al. 1990). The higher exposure group received poorer test scores in tests of visual retention, visual reproduction, trail making, grooved peg board, digit span, and digit symbol, but not on tests of simple reaction time and finger tapping.

Another group of 29 exposed workers in Singapore (average TWA toluene exposure of 90.9 ppm) performed more poorly than a control group (average TWA exposure of 12.2 ppm) on 8 neurobehavioral tests. The exposed group performed significantly more poorly in verbal and nonverbal memory as measured by the digit span and visual reproduction tests (Boey et al. 1997).

Low-level occupational exposure to an average of 97 ppm toluene for 12–14 years had an apparent effect on hearing in 40 rotogravure workers when brainstem auditory evoked potential (BAEP) results were compared to a group of 40 workers who were of comparable age but were not exposed to toluene (Abbate et al. 1993). Workers were carefully screened to eliminate slight hearing abnormalities or exposure to other chemicals. Two series of stimuli were used, one with 11 repetitions/second and one with 90 repetitions/second. In both cases the intensity was 80 dB/nHL. Mean latencies were significantly higher for the exposed group than the control group for each BAEP wave evaluated (I, III, and V). Discernment mean values for the exposed and control groups were distributed homogeneously with very little overlap of exposed and control responses for both the 11-repetition and 90-repetition cycles. Wave I showed the most pronounced increase in latency. According to the authors, the effects on Wave I could

be due to either a change in the membrane of the peripheral receptor, a modification of the structure of the junction, or a change in the stimulus transduction mechanism.

In two other studies, BAEPs in workers exposed to average concentrations of about 50 ppm for an average of 21.4 years were found to be affected, with a significant decrease in all wave amplitudes and a significant increase in all wave latencies except P2 (Vrca et al. 1995, 1997a).

In a cross-sectional examination of 124 Brazilian workers exposed to various levels of noise and a variety of organic solvents, including toluene at TWA concentrations ranging from 0.037 to 244 ppm, (midpoint=122 ppm), 49% of workers experienced hearing loss (Morata et al. 1997). Toluene exposure (and exposure to a number of other solvents including ethanol and ethyl acetate) was estimated by personal monitoring and measurement of hippuric acid in urine samples. Confidence in the study is limited because of exposure to multiple solvents and possible confounding from noise exposure. However, logistic regression analysis showed hippuric acid concentration to be significantly associated with hearing loss and the odds ratio estimates for hearing loss were 1.76 times greater for each gram of hippuric acid per gram creatinine (95% CI 1.00–2.98).

Occupational exposure to toluene may also affect other sensory-evoked potentials. Visual evoked potentials (P300, N75, N145, and P100 waves) in printers occupationally exposed to average concentrations of 50 ppm toluene for an average of 21 years were compared to those of unexposed controls (matched for alcohol and coffee consumption, smoking, age, years of work, education, and head injuries) (Vrca et al. 1995, 1997a, 1997b). Individual exposure was estimated by measuring toluene levels in blood (0.036 mg/L in exposed workers, 0.0096 mg/L in controls) and hippuric acid levels in urine (0.426 g/g creatine in exposed workers, 0.338 g/g creatine in controls). There was a significant increase in the number of exposed individuals displaying reduced amplitude of P300R waves and prolonged latency of the accompanying spontaneous wave P300F (Vrca et al. 1997b). The amplitudes of the N75, P100, and N145 waves (Vrca et al. 1995, 1997a), and the latency of the P100 wave, were significantly increased in exposed subjects compared with controls (Vrca et al. 1995).

Chronic exposure to toluene may also cause color vision loss. Zavalic et al. (1998a) examined color vision in 83 controls, 41 shoemakers, and 32 printers exposed respectively to geometric mean toluene concentrations of 0, 35, or 156 ppm. Toluene exposure was estimated by measuring toluene levels in the air and in the blood of workers, and by measuring the amount of hippuric acid and orthocresol in their urine at the end of the work shift. The technology, ventilation, and types of workplaces included in the study had not changed in the preceding 30 years. Color confusion was significantly higher in printers

compared with both shoemakers and controls. Color confusion index was increased in shoemakers compared with controls, but the difference was not significant (Zavalic et al. 1998a). Regression analysis established a significant correlation between color confusion as a dependent and alcohol intake and age as independent variables for the control group. Age- and alcohol-adjusted color confusion index was significantly increased in printers compared with shoemakers and controls, and in shoemakers compared with controls. After age and alcohol adjustments, individual color confusion indices were significantly correlated with individual exposure estimates (air, blood, or urine) in printers, but in shoemakers, the correlation was not statistically significant. The significantly increased color confusion index for the shoemakers in this study was assessed as a less-serious adverse effect and the LOAEL of 32 ppm served as the basis for the chronic-duration inhalation MRL, 1 ppm, for toluene (see footnote of Table 2.1, Section 2.5 and Appendix A).

Further analysis of color vision loss in the same groups of workers described above (Zavalic et al. 1998a) was carried out to compare loss in the blue-yellow and red-green ranges (Zavalic et al. 1998c). Both blue-yellow and red-green color confusion were significantly increased in printers, but there was no significant difference in the prevalence of either type of color confusion between exposed and unexposed workers (Zavalic et al. 1998c).

Color vision impairment was also evaluated in another group of 45 male workers exposed to mean concentrations of about 120 ppm toluene (Zavalic et al. 1998b). Color vision was significantly impaired in exposed workers compared with unexposed controls. A comparison of color vision assessments made on Monday and Wednesday mornings showed no significant difference. This suggests that color vision impairment results from chronic rather than acute exposure to toluene.

Muttray et al. (1995, 1999) also attempted to distinguish between effects on vision due to chronic and acute exposure to toluene. Color vision was assessed in 59 male rotogravure workers occupationally exposed to unspecified levels of toluene for periods of 1 month to 36 years (mean of 10 years) (Muttray et al. 1995). Results of vision testing at the beginning and end of the work week were compared and no difference was recorded. A second study compared color vision in eight printers (occupationally exposed to toluene) and eight workers previously unexposed to toluene, before and after cleaning a print machine with toluene (Muttray et al. 1999). The task took 28–41 minutes and involved exposure to 300–362 ppm toluene (1,115–1,358 mg/m^3). No impairment in color vision was recorded for either group. However, a comparison of the precleaning performance of the printers with that of a group of matched controls

showed a non significant decrease in color vision for the printers, which may indicate a chronic effect of toluene exposure on color vision (Muttray et al. 1999).

Studies of human color vision impairment suggest that vision impairment results from chronic, rather than acute, exposure to toluene (Muttray et al. 1995, 1999; Zavalic et al. 1998a, 1998b, 1998c). The mechanism by which toluene exposure influences color vision is not known. Visual evoked potentials are affected in chronically exposed individuals and show exposure-related changes in amplitude and latency (Poblano et al. 1996; Vrca et al. 1995, 1997a, 1997b). However, it is not clear whether the impairment of color vision produced by toluene exposure is due solely to neurological damage or also involves damage to the eyes. Toluene exposure causes eye irritation in humans (Andersen et al. 1983; Baelum 1990; Carpenter et al. 1944; Meulenbelt et al. 1990) and animals (Ono et al. 1976), but no studies were located that examined eyes for structural damage due to chronic toluene exposure.

A number of studies of humans chronically exposed to mixtures of solvents containing toluene provide supporting evidence for the neurotoxicity of toluene, but concurrent exposure to other solvents limits the conclusions that can be drawn from the results. Painters (100 individuals) exposed to toluene and other solvents for 1–40 years had poorer performance on the block design of visual cognitive ability (Hanninen et al. 1976). Another study of 325 painters exposed to mixed solvents (including toluene) for an average of 5 years found that reduced ability in tests of pattern comparison and memory was correlated with solvent-exposure (Tsai et al. 1997). Shoemakers exposed to toluene (20 or 71 ppm) and other solvents for more than 10 years showed a significant reduction in the Santa Ana dexterity test and a non significant reduction in visual retention (Lee et al. 1998a). Workers exposed to mixed solvents (including toluene) during a spraying process showed a significant impairment of color vision with errors of the blue-yellow type (Muttray et al. 1997). A study of chronic petrol sniffers found that petrol sniffing was associated with neurological and cognitive abnormalities such as tremors, abnormal reflexes, and deficits of visual attention and memory (Maruff et al. 1998). However, significant correlations were recorded for the magnitude of neurological and cognitive defects and blood lead levels, but not for neurological and cognitive defects and blood hydrocarbon levels (Maruff et al. 1998). A group of workers exposed to mixed solvents and admitted to the hospital due to suspicion of solvent-induced chronic toxic encephalopathy had reduced scores in tests of distorted speech and cortical response audiometry compared to unexposed controls (Niklasson et al. 1998).

In laboratory animals, acute exposure to toluene has both excitatory and depressant effects on the central nervous system. A high correlation between the extent of central nervous system depression and brain

toluene levels was observed in both mice and rats exposed to 2,600–12,000 ppm toluene for varying periods of time (Bruckner and Peterson 1981a, 1981b). Acute exposure to toluene concentrations between 500 and 15,000 ppm produced an initial increase in locomotor activity in rats and mice followed by a decrease in activity with longer exposure (Bowen and Balster 1998; Bushnell et al. 1985; Hinman 1987). Exposure of mice to 300 ppm for 6, 1-hour exposures with 3–4 days between exposures, had no effect on animal movements. Movements were increased at concentrations of 560–1,780 ppm, but were decreased at concentrations of 3,000 ppm (Wood and Colotla 1990). This study clearly indicates a biphasic response with low-concentration stimulation and high-concentration depression of motor activity.

Monkeys exposed to concentrations of 2,000–4,500 ppm toluene (head only) for 50 minutes on 2 days separated by 3 days without exposure, showed significantly increased response time and decreased accuracy on a test of conditioned response to a reward stimulus for concentrations (Taylor and Evans 1985). Exposure to toluene concentrations of 2,000 ppm or less did not cause overt signs of neurological impairment such as ataxia and tremors. Exposure to 100 and 200 ppm toluene had no effect on performance, but exposure to 500 and 1,000 ppm toluene caused nonsignificant decreases in response time and accuracy.

Exposure to 1,500 ppm toluene 1 hour/day for 14 days produced nystagmus (involuntary movement of the eyeballs) in rats with disturbances in the vestibular and opto-oculomotor systems (Larsby et al. 1986). These findings suggest that the cerebellum is a target site for toluene, and confirm an earlier report that toluene caused nystagmus in rats when arterial blood levels were greater than 75 ppm (Tham et al. 1982).

In several animal studies, acute toluene exposure diminished the ability of rats to perform trained neuromuscular responses. Exposure of rats to 125, 250, or 500 ppm toluene for 4 hours caused a decline in lever-press shock avoidance performance 20 minutes after exposure, but recovery was complete 2 hours later (Kishi et al. 1988). A single 4-hour exposure to concentrations of 810–6,250 ppm toluene caused a concentration-related impairment of performance by rats in tests designed to measure neuromuscular performance (Mullin and Krivanek 1982). Exposure to $480 ppm toluene for 4 hours decreased the ability of trained rats to perform a sequence of lever press actions associated with a reward (milk) (Wood et al. 1983).

In animals, changes in the levels of brain neurotransmitters in rodents exposed to toluene have been observed. Significant localized changes in dopamine (DA) or norepinephrine (NE) brain levels were

noted in rats exposed to 400 ppm toluene 24 hours/day for 30 days (Ikeda et al. 1986) and in newborn male rats 7 weeks after a 10-day exposure to 80 ppm toluene for 6 hours per day (von Euler et al. 1989b). Neurotransmitter levels in some areas of the brain were increased, in some areas were decreased, and in other areas remained the same. Toluene exposure at 80 ppm for 4 weeks was found to affect dopamine D_2 agonist binding in the rat caudate-putamen (Hillefors-Berglund et al. 1995; von Euler et al. 1993). Dopamine levels were increased in the cerebellum and striatum of rats exposed to 1,000– 4,000 ppm toluene for 20 minutes, while norepinephrine and 5-hydroxytryptamine were significantly increased in the cerebellum and cortex (Kim et al. 1998). Several significant changes in the activities of enzymes responsible for neurotransmitter synthesis (glutamic acid decarboxylase, choline acetyltransferase and aromatic amino acid decarboxylase) in different areas of the brain were seen in male rats exposed to toluene at concentrations of 50–1,000 ppm for 4 weeks or 500 ppm for 12 weeks (Bjornaes and Naalsund 1988). Concentration-response trends were not apparent in the data and there were variant responses by different areas of the brain. There was also some evidence of change in glutamate and gamma amino butyric acid (GABA) binding. Binding increased in most of the brain areas studied, but decreased in some areas. Because of the variability in response, these data are difficult to evaluate. Von Euler et al. (1994) reported that rats exposed to 80 ppm for 6 hours per day for 4 weeks, had increased serum prolactin levels. However, no significant changes in serum prolactin levels were reported at concentrations up to 320 ppm, also for 4 weeks exposure (Hillefors-Berglund et al. 1995). Exposure to 400 ppm toluene 7 hour/day for 10 days produced a statistically significant increase in the total dehydrogenase activity in the brains of female mice (Courtney et al. 1986).

Changes in brain levels of glial fibrillary acidic protein (GFAP), a structural marker for astrocytes, have been found in toluene-exposed rats. Rats exposed to 1,000 ppm toluene for 3 or 7 days exhibited a significant decrease in GFAP levels in the thalamus (Little et al. 1998). Rats exposed to 100–3,000 ppm toluene 6 hours/day, 5 days/week for up to 42 days exhibited changes in the concentration of GFAP in the cerebellum, hippocampus, and thalamus (API 1997). For the first week of exposure, GFAP concentration of exposed animals was significantly increased in the cerebellum and hippocampus, and decreased in the thalamus compared with unexposed controls (API 1997). After 21 days, the concentration of GFAP in the hippocampus was significantly decreased in rats exposed to 1,000 ppm compared with controls, while at 42 days, rats exposed to 300 ppm had significantly higher concentrations of GFAP in the cerebellum compared with controls, but rats exposed to 1,000 ppm did not (API 1997). In mice exposed to 500–2,000 ppm for 8 hours, no significant alterations in *c-fos*, *c-jun*, or GFAP mRNA in the cerebrum were found (Matsuoka et al. 1997).

Rats continuously exposed to toluene at 320 ppm for 30 days had decreased total brain weight and decreased weight of the cerebral cortex (Kyrklund et al. 1987). There was a decrease in the total phospholipid content of the cerebral cortex accompanied by a small increase in phosphatidic acid levels. These data suggest a breakdown of phospholipids resulting in a loss of gray matter (Kyrklund et al. 1987). The mechanism of action for this effect is uncertain. Increased relative brain weights and ataxia in rats were reported after 15-week exposures to toluene at 2,500 and 3,000 ppm 6.5 hours/day, 5 days/week (NTP 1990). No gross or microscopic tissue changes or changes in brain weights were observed in mice exposed to concentrations up to 2,500 ppm for 14 weeks or in rats or mice exposed by the same protocol to toluene at concentrations up to 1,200 ppm for 2 years (NTP 1990).

Animal studies have demonstrated that intermediate exposure to toluene can produce subtle changes in the auditory system. Intermediate exposure to toluene produced a permanent loss of hearing in the high frequency range (approximately 16 kHz) in rats exposed 14 hours/day to 1,200 ppm for 5–9 weeks or 1,000 ppm for 2 weeks (Pryor and Rebert 1992; Pryor et al. 1984a, 1984b). The threshold concentration for hearing loss was between 700 and 1,000 ppm (Johnson et al. 1988; Pryor et al. 1984b). Hearing loss occurred independent of whether or not exposure was continuous or episodic with many short exposures during the day (Pryor 1991); it was compounded by postexposure high noise levels (Johnson et al. 1988). Lataye and Campo (1997) demonstrated that combined exposure to toluene and noise produced a greater loss of hearing function in rats than exposure to toluene alone or noise alone. In another study, hearing loss was produced in rats after exposure to 1,750 ppm toluene for 6 hours/day, 5 days/week for 4 weeks and loss of hair cells in the organ of corti was observed after exposure to 1,000 ppm (Campo et al. 1997, 1998). Johnson and Canlon (1994) showed loss of outer hair cells in the cochleae of rats exposed to 1,400 ppm 14 hours/day for 8 days. Outer hair cell loss was observed after 5 days of exposure, and loss progressed to the inner hair cells after 6 weeks postexposure. Pryor et al. (1984a) demonstrated that high frequency hearing loss is more severe in weanling rats than in young adult rats, after exposure to 1,200 ppm for 14 hours/day for 5 weeks. Hearing loss due to toluene exposure was also exacerbated by simultaneous treatment with ethanol (Campo et al. 1998) or high doses of acilyl solicylicacid (aspirin) (Johnson 1992).

When rats were preexposed to phenobarbital to stimulate liver metabolism of toluene and then exposed to levels of 1,929 ppm 8 hours/day for 1 week, hearing was not affected as measured by the BAER test (Pryor et al. 1991). However, rats not pretreated with phenobarbital did experience hearing loss. This observation is consistent with the idea that toluene itself, and not one of its metabolites, is responsible for the hearing loss.

Toluene had more of an effect on hearing loss in mice that had a genetic predisposition for early onset spontaneous auditory degeneration than on mice that were predisposed to late onset moderate hearing loss (Li et al. 1992). Thus, the severity of toluene-induced hearing loss appears to be influenced by genetic susceptibility.

Impaired motor functions have been observed in animals following repeated exposure to toluene. Daily exposure of neonate rats to 10,000, 20,000, or 40,000 ppm toluene for 15 minutes from postpartum days 2–30 resulted in a concentration-related increase in the time taken for the righting-reflex to occur (Lorenzana-Jimenez and Salas 1990). At each concentration, the time taken for the righting-reflex to occur decreased over the first 4 weeks of exposure then increased over the last 4 weeks of exposure, but did not regain the level of latency observed in the first week of the experiment. These data suggest that these animals were developing tolerance to some neurobehavioral effects of toluene. However, it is not clear whether this is due to metabolic induction by continued exposure or an age related effect.

Tilting plane and rotarod test performances did not differ significantly between control rats and rats exposed to 1,000 ppm toluene for 8 hours/day, 7 days/week for 13 weeks (Tahti et al. 1983). Rats exposed to 2,500 ppm toluene 7 hours/day for 5 weeks showed a lack of coordination (Von Oettingen et al. 1942). Exposure of rats to concentrations of 2,273 ppm 8 hours per day for 16 weeks or to 2,200–6,200 ppm intermittently (8 hours/day, 15–60 minutes/hour) for 23 weeks caused a shortening and widening of the gait (Pryor 1991). Increased nose-poking was reported in rats exposed to 178–300 ppm toluene for 3 weeks (2 times/week, 2 hours/day) (Wood and Cox 1995). Latency of escape from an electric shock was reduced in both young rats (50 days old) and older rats (120 days old) exposed to 30,000–40,000 ppm toluene for 15 minutes/day for 30 days (Castilla-Serna et al. 1991). Exposure of male weanling rats (23 days old) to 1,200 ppm 14 hours/day for 9 weeks produced a significant reduction in a tone-induced multisensory conditioned avoidance response (Pryor and Rebert 1992).

Circadian rhythms apparently have an effect on toluene metabolism and, thus, on its neurological effects. Rats that were exposed to 4,000 ppm toluene for 4 hours during daylight demonstrated poorer shock avoidance than animals exposed during the dark (Harabuchi et al. 1993). There was a correlation of shock avoidance with toluene levels in the brain; the higher the brain toluene level, the poorer the ability of the animal to properly respond to stimuli and press the lever that prevented the electrical shock.

Flash evoked potential (FEP) responses were abnormal in rats exposed to single 30-minute exposures to 500–16,000 ppm toluene (Rebert et al. 1989a, 1989b) or 15 to 35 minute exposures to 8,000 ppm,

4–9 times/day, 5 days/week for 13 weeks (Mattsson et al. 1990). This technique measures the electrical response of the visual components of the nervous system to a high intensity flashing strobe light. Distortion of the FEP waveform is indicative of impaired visual response to light. In both the acute and subchronic testing situations, the toluene caused changes in the amplitude of several components of the FEP waveform, suggesting that impaired visual response can result from both short and long term exposure to high concentrations of toluene.

Toluene exposure also changes sleep patterns in animals. Both single 4- or 8-hour episodes of toluene exposure (900–4,000 ppm) and repeated exposures, 8 hour/day for 3 weeks (900 and 2,700 ppm), changed patterns of sleep and wakefulness in rats (Arito et al. 1988; Takeuchi and Hisanaga 1977). After the single exposures, there was a decrease in wakefulness and an increase in slow-wave sleep; a prolonged sleep latency was apparent for the 2 days following exposure. Latency was defined as the time interval between the end of the exposure period and the beginning of a particular phase of the sleep cycle. Following the 3-week exposures, there was an increase in wakefulness during the dark period on the 2 days after exposure and a decrease in slow wave sleep on the first day. Exposure to concentrations of 100–700 ppm for 2 hours increased the duration of the wake cycle and decreased both rapid-eye movement and nonrapid eye movement sleep in a concentration-related fashion in young and adult male rats (Ghosh et al. 1989, 1990).

Toluene may affect memory in rats. Rats exposed to 600 ppm toluene for 50 days, starting at 23 days old, were trained in a radial-arm maze and their performance was compared with air-exposed control animals. No significant effects were observed for working memory errors (reentries into “already-entered” areas) (Miyagawa et al. 1995). However, rats exposed to 1,600 or 3,200 ppm toluene for 4 hours showed a concentration-related decrease in accuracy in a neurological test of short-term memory (Miyagawa et al. 1998). Exposure to 1,500 ppm toluene 6 hours/day, 5 days/week for 6 months followed by a 4-month exposure-free period was found to reduce the number of neurons in the rat hippocampus, an important area in the brain for memory and learning processes (Korbo et al. 1996).

The highest NOAEL values and all LOAEL values for each reliable study for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

Current data do not provide convincing evidence that toluene causes reproductive effects in humans. Reports that occupational exposure to toluene may lead to an increased incidence of spontaneous abortion (Ng et al. 1992b; Taskinen et al. 1989) have not been supported by the results of animal testing. Studies in rats have shown no evidence of adverse effects on mating or fertility (API 1985; NTP 1990; Ono et al. 1996). Toluene exposure produced microscopic changes in ovarian structure and a reduction in sperm count and the weight of epididymides in rats (Ono et al. 1996; Tap et al. 1996). However, changes in sperm count and epididymus weight were not accompanied by any change in indices of reproductive performance (Ono et al. 1996).

Ng et al. (1992b) reported a significant increase in spontaneous abortion for women employed in an audio speaker factory and exposed to 50–150 ppm (mean of 88 ppm) for 10 years (12.4%), compared with controls exposed to 0–25 ppm toluene from the same factory (2.9%) and unexposed controls from the general population (4.5%). The majority of women examined did not smoke or drink and were of similar socioeconomic status (Ng et al. 1992b). Exposed workers did not report increased incidence for menstrual cycle irregularities, altered extent of uterine bleeding, or occurrence of dysmenorrhea (Ng et al. 1992a). Other possible confounding factors such as exposure to chemicals other than toluene were minimized by inclusion of controls who carried out similar types of work, but did not use toluene-based adhesives (Ng et al. 1992b).

The incidence of spontaneous abortions exceeded population norms among 5 female workers (Lindbohm et al. 1992) and among the wives of 28 or 48 male workers (Lindbohm et al. 1992; Taskinen et al. 1989) exposed to toluene; however, exposure levels were not reported in these studies and only a small number of cases were included. A study of time to pregnancy among the wives of 316 men occupationally exposed to mixed organic solvents found that paternal exposure to organic solvents was significantly correlated with decreased fecundability of primagravida, but not among couples with at least one previous pregnancy (Sallmen et al. 1998). The significance of these studies is limited by the failure to account for the large number of possible confounding factors such as smoking, alcohol consumption, and exposure to mixed chemicals.

Changes in human gonadotropic hormone levels have been associated with toluene exposure. A single case report of testicular atrophy involving chronic solvent abuse was located (Suzuki et al. 1983). Exposure to increasing concentrations of toluene (8–<111 ppm) was associated with decreased plasma

levels of the luteinizing hormone, follicular stimulating hormone, and testosterone levels in 20 or 47 males occupationally exposed for 0.5–39 years to average toluene concentrations of 36 or 29 ppm (Svensson et al. 1992a, 1992b). It is not clear how changes of this sort would affect reproductive success. Interpretation of these data is complicated by the lack of data on male reproductive function. It is generally considered that effects of this sort may be the result of effects of toluene on the catecholamine hormones of the hypothalamus or a consequence of toluene or a metabolite having a dopamine-like activity. Thus, it appears that any potential toluene-induced hormonal effects on reproductive success which may occur may be secondary to effects on the central nervous system.

Significantly decreased sperm counts (26%) and decreased weights of the epididymides (15%) were reported in male rats exposed to 2,000 ppm 6 hours/day for a total of 90 days, including 60 days before mating to females that were exposed for 14 days before and 7 days after mating (Ono et al. 1996). A slight decrease in sperm count (13%) was also observed at 600 ppm, but histological examination of the testes and epididymes found no abnormalities at either concentration. No significant exposure-related effects on mating behavior or fertility indices were found in this study (Ono et al. 1996). Exposure of female rats to 3,000 ppm toluene for 7 days produced abundant vacuoles, lytic areas, and mitochondrial degeneration in the antral follicles of the ovaries (Tap et al. 1996).

The administration of toluene to male mice at concentrations of 100 or 400 ppm for 8 weeks did not induce dominant lethal mutations or cause pre- and postimplantation losses (API 1981). There were no treatment-related histopathological lesions in the testes of rats and mice exposed to up to 3,000 ppm toluene for 14–15 weeks although rats showed a 15% increase in testis weight (NTP 1990). Similarly, toluene did not cause histopathological lesions of the ovaries or testes in rats exposed to toluene (300 ppm) for 24 months (CIIT 1980) or in rats and mice at concentrations of 1,200 ppm for 2 years (NTP 1990). Continuous exposure of pregnant rabbits to 267 ppm during days 7–20 of pregnancy produced maternal toxicity (decreased weight gain) and abortions in 4/8 does, but no effect was observed with exposure to 133 ppm (Ungvary and Tatrai 1985). Exposure of mice to 267 ppm, 3–4 hours/day on days 6–15 of gestation produced no increase in fetal mortality (Ungvary and Tatrai 1985).

In 2-generation reproduction studies in rats, exposure to 2,000 ppm 6 hours/day for up to 95 days did not adversely affect reproductive parameters or offspring survival compared with unexposed controls (API 1985). Another rat study found no effects on mating, fertility, or pregnancy indices for F_1 rats that had been exposed *in utero* to 1,200 ppm toluene for 6 hours/day during gestation days 9–21 (Thiel and Chahoud 1997).

The highest NOAEL values and all LOAEL values for each reliable study for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

Case reports of birth defects in children of mothers who abused toluene during pregnancy and a report of nervous system defects in Finnish women exposed to mixed solvents in their workplace suggest that exposure to high levels of toluene may be toxic to the developing fetus, but cannot support definitive conclusions because of the lack of exposure data and the inability to adjust for confounding exposures to other potential developmental toxicants.

A retrospective study of 14 women in Finland occupationally exposed to mixed solvents, some of which included toluene, and also exposed to various drugs including aspirin, vasodilators, and diuretics suggested that solvent exposure may increase the risk of central nervous system anomalies and defects of neural tube closure in children exposed *in utero* (Holmberg 1979). However, the sample size was too small to be truly meaningful.

Microcephaly, central nervous system dysfunction, attentional deficits, minor craniofacial and limb anomalies, developmental delay, and variable growth have been described in case reports of children who were exposed to toluene *in utero* as a result of maternal solvent abuse during pregnancy (Arnold and Wilkins-Haug 1990; Arnold et al. 1994; Hersh 1988; Hersh et al. 1985; Lindemann 1991; Pearson et al. 1994; Wilkins-Haug and Gabow 1991a). Growth retardation and dysmorphism were reported in five infants born to women who were chronic paint sniffers (Goodwin 1988).

Children born to toluene abusers have exhibited renal tubular acidosis immediately after birth that is thought to be due to alterations in ion gradient maintenance in the renal tubules. The kidney effects are often associated with hyperchloremia (Erramouspe et al. 1996; Goodwin 1988; Lindemann 1991). In one report (Goodwin 1988) the acidosis was resolved within 3 days of birth, while in the other two reports, it took about 2 weeks for the resolution of the metabolic acidosis. There were no abnormalities in the urinary tract of two children born to chronic toluene abusers based on results of a renal ultrasound evaluation (Hersh 1988).

A number of developmental toxicity studies with rats, mice, and rabbits involving toluene exposure during gestation have been conducted to further describe developmentally toxic effects from toluene and

exposure-response relationships. In general, the results indicate that toluene is not a potent teratogenic agent at exposure levels below those inducing maternal toxicity, but can retard fetal growth and skeletal development and alter development of behavior in offspring.

In pregnant rats exposed to 399 ppm, 24 hours/day on gestation days 1–8 or 9–14, no statistically significantly increased incidences of fetuses with visceral or skeletal malformations were found (Hudak and Ungvary 1978). However, 5/14 dams died, fetal body weight was decreased, and retardation of fetal skeletal development occurred with the days 1–8 exposure protocol, and 2/21 dams died and increased incidence of skeletal anomalies (extra ribs, fused sternebrae) were found with the days 9–14 protocol (Hudak and Ungvary 1978). No maternal mortality, fetal weight loss, or fetal malformations were found in another group of rats exposed to 266 ppm, 8 hours/day on gestation days 1–21, but significantly increased incidence of fetuses with skeletal retardation occurred (Hudak and Ungvary 1978). In other groups of rats exposed to 250, 750, 1,500, or 3,000 ppm, 6 hours/day on gestation days 6–15, no effects were found on maternal or fetal survival, but mean fetal body weights were significantly decreased by about 8–14% at 1,500 and 3,000 ppm and the percentage of fetuses with unossified sternebrae was significantly increased at 3000 ppm (60 versus 37% in controls) (Huntingdon Research Centre 1992b). Incidences of fetuses or litters with skeletal or visceral malformations were slightly increased to a statistically significant extent in the 250-, 1,500-, and 3,000-ppm groups, but the response did not increase with exposure level, indicating that it was not exposure-related (Huntingdon Research Centre 1992b). A preliminary gestational exposure study that did not include comprehensive examination for skeletal and visceral fetal variations and malformations found extreme maternal toxicity and marked resorption of fetuses in pregnant rats exposed to 5,000 ppm 6 hours/day on gestation days 6–15, and significantly decreased mean fetal body weight in a 3,500-ppm exposed group (by about 20% compared with controls) (Huntingdon Research Centre 1992a). No statistically significant effects on maternal or fetal survival, implantation, numbers or incidences of fetuses or litters with skeletal or visceral malformations, anomalies, or variations were found in pregnant rats exposed to 600 or 2,000 ppm, 6 hours/day on gestation days 7–17, but maternal and fetal body weights were reduced in the 2,000 ppm group compared with controls (Ono et al. 1995). Offspring of rats exposed to 1,200 ppm toluene, 6 hours/day on gestation days 9–21 showed a significant reduction in fetal weight, a delay in physical development (vaginal opening) and higher mortality until weaning compared to unexposed controls (Thiel and Chahoud 1997). Rats exposed to 1,000 ppm, 6 hours/day on gestation days 9–21 also had significantly reduced body weights at birth and developmental delay, but no effect on fetal weight or development was recorded for rats exposed to 300 or 600 ppm.

In mice exposed to 133 ppm, 24 hours/day on gestation days 6–13, no effects on maternal survival or incidences of fetuses with malformations were found, but fetal body weight was significantly decreased (Hudak and Ungvary 1978). All 15 pregnant mice died that were exposed to 399 ppm, 24 hours/day on gestation days 6–13 (Hudak and Ungvary 1978). Exposure of pregnant mice to 133 or 266 ppm, 3–4 hours/day on gestation days 6–15, did not significantly affect maternal or fetal survival, or incidences of fetuses with visceral or skeletal anomalies or malformations, but, in the group exposed to 266 ppm, incidences of fetuses with decreased body weight and skeletal retardations were significantly increased (Ungvary and Tatrai 1985). Other groups of pregnant mice exposed to 200 or 400 ppm, 7 hours/day on gestation days 7–16 showed no statistically significant differences from controls in maternal or fetal survival, maternal or fetal body weights, and the number of implantation sites or live fetuses (Courtney et al. 1986). Significantly increased incidence of fetuses or litters with visceral or skeletal anomalies or malformations were restricted to increased litters with fetuses with enlarged renal pelves in the 200-ppm group (but not in the 400-ppm group) and a difference in the distribution of fetuses with varying numbers of ribs in the 400-ppm group compared with the control group. Courtney et al. (1986) suggested that these effects may be due to toluene-induced "desynchronization of growth and maturation" of the developing fetus. Offspring, evaluated 21 days after birth, of a separate group of pregnant mice exposed to 400 ppm toluene by the same protocol showed no significant differences from control offspring in body or organ weights or activities of lactate dehydrogenase in several tissues, except that brain activities of this enzyme were elevated (Courtney et al. 1986).

In rabbits exposed to 133 ppm, 24 hours/day on gestation days 7–20, no significant effects were found on maternal or fetal survival, fetal body weight, or incidences of fetuses with skeletal retardation, minor anomalies, or skeletal or visceral malformations (Ungvary and Tatrai 1985). Following exposure to 266 ppm by the same protocol, 2/8 dams died, 4/8 dams aborted, and no live fetuses were found at sacrifice (Ungvary and Tatrai 1985). In other groups of rabbits exposed to 30, 100, 300, or 500 ppm, 6 hours/day on gestation day 6–18, no signs of maternal toxicity occurred and no significant effects, compared with controls, were found on fetal weight or survival, pre- or postimplantation losses, or incidences of fetuses with external, soft-tissue, or skeletal variations or malformations (Klimisch et al. 1992).

Results from studies of neurobehavioral end points in rats following *in utero* exposure to toluene suggest that maternal exposure to concentrations above 1,200 ppm, 6 hours/day during late embryonic and fetal development can impair behavioral development of rat offspring. Rat pups, that were evaluated on postnatal days 1–20 and whose mothers were exposed to 2,000 ppm for 60 minutes, 3 times/day on

gestation days 12–17, gained less weight and displayed significant performance deficits in neurobehavioral tests of reflex development, muscle strength, and motor coordination (Jones and Balster 1997). These effects were not observed in offspring of dams exposed to 200 or 400 ppm by the same protocol (Jones and Balster 1997). Rat offspring of dams exposed to 600 or 2,000 ppm, 6 hours/day on gestation days 7–17 showed no significant differences from control rats in tests of reflexes, locomotor activity, balance on a rotating rod, learning ability, or in physical development (e.g., eye opening) during the first 5 days after birth (Ono et al. 1995). No consistent and concentration-dependent performance deficits were found in tests of reflexes, balance on a rotating rod, locomotor activity, or discrimination learning in rat offspring, evaluated at several ages, of dams exposed to 300, 600, 1,000, or 1,200 ppm, 6 hours/day on gestation days 9–21 compared with controls (Thiel and Chahoud 1997).

In groups of rat pups exposed to toluene (100 or 500 ppm, 12 hours/day) from postnatal days 1–28, the volumes of the granular cell layer of the area dentate of the hippocampus were smaller (6 and 13%, respectively) compared to unexposed controls (Slomianka et al. 1990). However, when animals in the 500 ppm group were allowed to recover for 92 days after exposure ceased, these effects were reversible (Slomianka et al. 1992). The authors attributed this response to desynchronization in growth and maturation.

The highest NOAEL values and all LOAEL values for each reliable study for developmental effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

Human data are inconclusive with regard to the genotoxicity of toluene. Studies of exposed workers are limited by concurrent exposure to other chemicals, small cohort size, and a lack of historical exposure monitoring, and it is likely that they are not sufficiently sensitive to detect small, but significant, manifestations of genetic toxicity in toluene exposed workers. Genotoxicity testing of laboratory animals *in vivo* has been limited and has produced mostly negative results. Negative results were also reported in the *in vitro* studies discussed in Section 2.5.

An analysis of chromosome abnormalities in peripheral lymphocytes of printers exposed to 104 to 1,170 ppm toluene and unexposed workers from the same and nearby sites found an increase in chromosome breaks and aberrant cells in lymphocytes of exposed workers (Pelclová et al. 1990). Hammer et al. (1998) reported a concentration-related increase in sister chromatid exchange in

lymphocytes of printers exposed to 141–328 mg/m^3 (38–87 ppm) airborne toluene (measured by personal monitor). Chromosome analysis of lymphocytes of workers exposed to 200–300 ppm toluene in a rotogravure printing plant found a significantly increased frequency of sister chromatid exchanges and chromatid breaks compared to unexposed controls (Bauchinger et al. 1982). Re-examination of workers from the same plant after cessation of exposure to toluene found that more than 2 years without exposure was necessary to remove a significantly higher incidence of chromatid-aberrations in workers than in never-exposed controls (Schmid et al. 1985). Lymphocytes from printers exposed to a median time-weighted air level of 150 mg/m^3 (40 ppm) toluene per week were found to be significantly more sensitive to the production of micronuclei after stimulation with pokeweed mitogen than lymphocytes from unexposed controls (Nise et al. 1991).

A study of DNA damage in Bulgarian shoe workers exposed to factory air containing 96.0–412.3 mg/m^3 toluene (28–121 ppm) found no exposure related differences in DNA damage in leukocytes as assessed by the Comet assay (Pitarque et al. 1999). Toluene did not induce sister chromatid exchanges in lymphocytes of volunteers exposed to 50 ppm airborne toluene for 7 hours/day for 3 days on 3 occasions at 2 week intervals (Richer et al. 1993). Other investigators have also found no correlation between chronic occupational exposure to toluene and increased frequencies of either chromosome aberrations (Haglund et al. 1980; Maki-Paakkanen et al. 1980) or sister chromatid exchanges (Haglund et al. 1980).

In vivo tests of toluene in laboratory animals have produced mixed results. Exposure to toluene vapor induced mitotic arrest (C-mitosis) in embryos of the grasshopper, *Melanoplus sanguinipes* (Liang et al. 1983). Toluene was reported to induce chromosomal aberrations in the bone marrow cells of rats following exposure by inhalation (Dobrokhotov and Enikeev 1977). Toluene did not induce DNA damage in the blood, bone marrow, or liver of mice exposed to 500 ppm toluene for 6 hours/day, 5 days/week for eight weeks (Plappert et al. 1994). Toluene did not induce dominant lethal mutations in sperm cell of mice exposed to 400 ppm for 6 hours/day, 5 days/week for 8 weeks, but female mice were not assessed for genotoxic effects (API 1981). Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Eleven human epidemiology studies were located that assessed toluene exposure as a possible risk factor for cancer. Cancers of most sites were not significantly associated with toluene exposure in any study and there was weak consistency in the findings of those studies that did find association of a particular cancer type with toluene exposure. Three cohort studies involved occupationally exposed workers

exposed predominantly to toluene (Antilla et al. 1998; Svensson et al. 1990; Walker et al. 1993), whereas the remainder of the human studies primarily involved subjects exposed to mixtures of solvents including toluene (Austin and Schnatter 1983; Blair et al. 1998; Carpenter et al. 1988; Gérin et al. 1998; Lundberg and Milatou-Smith 1998; Olsson and Brand 1980; Wen et al. 1985; Wilcosky et al. 1984). The information from these studies is inadequate to assess the carcinogenic potential of toluene, predominantly because of the lack of consistent findings across the studies and the likelihood that many of the studied groups were exposed to multiple chemicals.

Svensson et al. (1990) compared cancer incidence and mortality in a cohort of Swedish printers, exposed primarily to toluene and employed for at least 3 months between 1925 and 1985, to mortality and cancer incidence for the region. Current and historical monitoring data were used to estimate yearly average concentrations of toluene in the air. Concentrations had declined from about 450 ppm in the 1940s to 30 ppm by the mid-1980s. There were indications of excess risk of morbidity (standardized incidence ratio, SIR) and mortality (standardized morbidity ratios, SMR) for respiratory tract cancer (SMR, 1.4; 95% CI, 0.7–2.5; n=11; SIR, 1.8; 95% CI, 1.0–2.9; n=16), stomach cancer (SMR, 2.7; 95% CI, 1.1–5.6; n=7; SIR, 2.3; 95% CI, 0.9–4.8; n=7) and colo-rectal cancer (SMR, 2.2; 95% CI, 0.9–4.5; n=7; SIR, 1.5; 95% CI, 0.7–2.8; n=9), but there was no significant association between increased risk and cumulative exposure.

Walker et al. (1993) conducted a cohort mortality study among 7,814 shoe-manufacturing workers (2,529 men and 5,285 women) from two plants in Ohio in operation since the 1930s. Workers were exposed to solvents and solvent-based adhesives. Based on results of a hygiene survey (1977–1979), exposure was thought to be primarily to toluene (10–72 ppm), but other chemicals (e.g., 2-butanone, acetone, and hexane) were also recorded at similar concentrations. IARC (1999) noted that benzene may have been present as an impurity of toluene. Mortality follow up was from 1940 to 1982 and relative risk estimates (SMRs) were derived using the general population of the United States as controls. There were excess risks of lung cancer for both men (SMR, 1.6; 95% CI, 1.2–2.0; n=68) and women (SMR, 1.3; 95% CI, 0.9–1.9; n=31), but smoking may have been a confounding factor and relative risk of lung cancer did not increase with increasing duration of employment. There was a slight excess risk for colon cancer among men (SMR, 1.3; 95% CI, 0.8–2.1; n=18) and women (SMR, 1.2; 95% CI, 0.8–1.8; n=28). Other cancers showed no excess risk.

Antilla et al. (1998) carried out a retrospective cohort analysis of 5,301 workers (3,922 male and 1,379 female) monitored for biological markers of occupational exposure to styrene, toluene or xylene

over the period 1973–1992. No increase in overall cancer risk or risk for cancers at specific tissue sites was associated with exposure to toluene, except for a non significant increase in the incidence of lung cancer in individuals exposed to toluene for more than 10 years (SIR, 1.62; 95% CI, 0.33–4.73; 3 cases). Antilla et al. (1998) noted, however, that these workers may also have been exposed to benzene.

Many of the other human epidemiological cancer studies showed positive associations between exposure to toluene and cancer at one or more tissue site, but individuals were exposed to multiple chemicals in all of these studies (Austin and Schnatter 1983; Blair et al. 1998; Carpenter et al. 1988; Gérin et al. 1998; Lundberg and Milatou-Smith 1998; Olsson and Brandt 1980; Wen et al. 1985; Wilcosky et al. 1984). Nested case-control studies included studies of prostate and brain cancer within cohorts of Texas petrochemical plant workers (Austin and Schnatter 1983; Wen et al. 1985), of lung cancer, stomach cancer, and leukemia among U.S. rubber workers (Wilcosky et al. 1984), cancer of the central nervous system among a group of Tennessee nuclear facility workers (Carpenter et al. 1988), prostate cancer and multiple myeloma among Swedish paint industry workers (Lundberg and Milatou-Smith 1998), and multiple myeloma, nonHodgkin's lymphoma, and breast cancer among aircraft maintenance facility workers (Blair et al. 1998). Community-based case-control studies examined possible associations between Hodgkin's disease in Swedish patients and controls (Olsson and Brandt 1980) and several cancer types in Canadian patients and controls (Gérin et al. 1998).

Inhalation cancer bioassays carried out in experimental animals have produced no evidence to support toluene as a potential carcinogen. No increased incidences of treatment-related neoplastic lesions were observed in Fischer 344 rats or $B_6C_3F_1$ mice exposed to toluene concentrations up to 1,200 ppm for 6.5 hours/day, 5 days/week for 2 years (NTP 1990). Similar results were reported for another study in which Fischer 344 rats were exposed to toluene concentrations up to 300 ppm 6 hours/day, 5 days/week for 2 years, but the maximum exposure concentration in this study was likely below that necessary to approach a maximum tolerated dose (CIIT 1980). The NTP (1990) study was well conducted, achieved the maximum tolerated dose, and provides evidence suggesting a lack of carcinogenicity of toluene in experimental animals.

2.2.2 Oral Exposure

Studies of the effects of oral exposure to toluene are limited. Only one study was located regarding health effects in humans after oral exposure to toluene and there are only a minimal number of animal studies.

2.2.2.1 Death

Ingestion of approximately 60 mL (625 mg/kg) of toluene proved fatal for a 51-year old male (Ameno et al. 1989). Death occurred within 30 minutes of ingestion. The autopsy results revealed constriction and necrosis of the myocardial fibers, a markedly swollen liver, congestion and hemorrhage of the lungs, and acute tubular kidney necrosis. The probable cause of death was determined to be severe depression of central nervous system function.

The limited number of studies on the acute oral toxicity of toluene in animals have focused on lethal effects. The acute oral LD_{50} of toluene in adult rats ranged from 5.5 to 7.4 g/kg (Kimura et al. 1971; Smyth et al. 1969; Withey and Hall 1975; Wolf et al. 1956). Age may play a role in determining the lethal dose for toluene. The LD_{50} value for 14-day-old rats was 3.0 g/kg, which is markedly lower than the adult values (Kimura et al. 1971).

Mice were more sensitive than rats to the lethal effects of toluene in 13-week gavage studies. All rats and mice that received 5,000 mg/kg died within the first week. Mortality was also high for groups receiving 2,500 mg/kg with eight out of ten male rats, one out of ten female rats, and with four out of ten male and female mice dying before the end of the study. A dose of 1,250 mg/kg/day was lethal in 10% of female mice but no deaths occurred in male mice or in rats of either sex (NTP 1990). LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Human data pertaining to the systemic effects of oral exposure to toluene are limited to two case studies (Ameno et al. 1989; Einav et al. 1997). Animal data are also limited, but include cardiovascular, hematological, hepatic, and renal effects in animals exposed orally to toluene at dosage levels up to 2,500 mg/kg/day for 13 weeks, or 590 mg/kg/day for 6 months (Hsieh et al. 1989; NTP 1990; Wolf et al. 1956). Exposure of rats or mice to toluene doses #2,500 mg/kg/day for 13 weeks was not found to produce any musculoskeletal, gastrointestinal or respiratory effects (NTP 1990). All systemic effects are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Table 2-2. Levels of Significant Exposure to Toluene - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
	ACUTE EXPOSURE							
	Death							
1	Human	once				625	(death in 30 minutes)	Ameno et al. 1989
2	Rat (Sprague-Dawley)	NS (G)				2610	(LD_{50} 14 day-old rat)	Kimura et al. 1971
3	Rat (Sprague-Dawley)	NS (G)				5568	(LD_{50} young adult rat)	Kimura et al. 1971
4	Rat (Sprague-Dawley)	NS (G)				6438	(LD_{50} adult rat)	Kimura et al. 1971
5	Rat	NS (G)				7300	(LD_{50})	Smyth et al. 1969
6	Rat	once (G)				5580 M	(LD_{50} adult rats)	Withey and Hall 1975
7	Rat (Wistar)	once (G)				7000	(LD_{50} young adult rats)	Wolf et al. 1956

Table 2-2. Levels of Significant Exposure to Toluene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference
	Systemic						
8	Human	once	Resp			625 M (lung congestion and hemorrhage)	Ameno et al. 1989
			Cardio			625 M (necrosis of myocardial fibers)	
			Gastro	625 M			
			Hepatic			625 M (enlarged liver)	
			Renal			625 M (acute tubular necrosis)	
9	Rat (Sprague-Dawley)	Gd 6-19 1x/d (GO)	Bd Wt			520 F (24% decrease in maternal body wt gain)	Gospe et al. 1994
	Neurological						
10	Rat (Long- Evans)	once (GO)			250[b] M (decrease in amplitude in FEP N3 peak)		Dyer et al. 1988
11	Rat (Sprague-Dawley)	once (G)			2610 M (increase in motor activity, lacrimation and salivation)		Mehta et al. 1998
	Reproductive						
12	Mouse (CD-1)	Gd 7-14 1x/d (GO)		2350 F			Smith 1983
	Developmental						
13	Rat	Gd 6-19				650 (reduced brain development of fetus)	Gospe and Zhou 1998

Table 2-2. Levels of Significant Exposure to Toluene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
14	Rat (Sprague-Dawley)	Gd 6-19 1x/d (GO)			520 (9.4% reduction in fetal weight)		Gospe et al. 1994
15	Rat (Sprague-Dawley)	Gd 6-19 1x/d (GO)				650 (11.9% decrease in fetal brain weights, 21% decrease in fetal weights, delayed skeletal ossification)	Gospe et al. 1996
16	Mouse (ICR)	Gd 8-12 5 d (G)		1800			Seidenberg et al. 1986
17	Mouse (CD-1)	Gd 7-14 1x/d (GO)		2350			Smith 1983
	INTERMEDIATE EXPOSURE						
	Death						
18	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d (GO)				2500 (80% of males and 10% of females died)	NTP 1990
19	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d (GO)				1250 F (1/10 died) 2500 M (4/10 died)	NTP 1990

Table 2-2. Levels of Significant Exposure to Toluene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Systemic						
20	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d (GO)	Resp	2500			NTP 1990
			Cardio	625 F 1250 M	1250 F (11% increase in relative heart weight) 2500 M (38% increase in relative heart weight)		
			Gastro	2500			
			Hemato	2500			
			Musc/skel	2500			
			Hepatic	312 M 625 F	625 M (8% increase in liver weight) 1250 F (22% increase in liver weight)		
			Renal	312 M 625 F	625 M (6% increase in kidney weight) 1250 F (8% increase in kidney weight)		
			Endocr	2500			
			Bd Wt	1250 M 2500 F	2500 M (body weight 19% lower than controls)		
21	Rat (Wistar)	6 mo 5 d/wk 1x/d (G)	Resp	590 F			Wolf et al. 1956
			Cardio	590 F			
			Hemato	590 F			
			Hepatic	590 F			
			Renal	590 F			

Table 2-2. Levels of Significant Exposure to Toluene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference
22	Mouse (CD-1)	28 d (W)	Hemato	105 M			Hsieh et al. 1989
			Hepatic	22 M	105 M (significant increase in liver weight-19%)		
			Renal	105 M			
			Bd Wt	105 M			
23	Mouse (CD-1)	28 d (W)	Bd Wt	105 M			Hsieh et al. 1990b
24	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d (GO)	Resp	2500			NTP 1990
			Cardio	2500		5000 (myocardial degeneration)	
			Gastro	2500			
			Hemato	2500			
			Musc/skel	2500			
			Hepatic	625 M	312 F (7% increase in relative liver weight) 1250 M 10% increase in relative liver weight)		
			Renal	2500			
			Endocr	2500			
			Bd Wt	625 M 2500 F	1250 M (body weight 16% lower than controls)		
	Immunological/Lymphoreticular						
25	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d (GO)		2500			NTP 1990

Table 2-2. Levels of Significant Exposure to Toluene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
26	Mouse (CD-1)	28 d (W)		22 M		105 M (diminished immune response)	Hsieh et al. 1989
27	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d (GO)		2500			NTP 1990
	Neurological						
28	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d (GO)		625		1250 (brain necrosis)	NTP 1990
29	Mouse (CD-1)	28 d (W)			5 [c] M (significantly increased levels of norepinephrin & dopamine in brain)		Hsieh et al. 1990b
30	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d (GO)		625 M	1250 M (12% increase in relative brain weight)	2500 (ataxia, hypoactivity, prostration)	NTP 1990

Table 2-2. Levels of Significant Exposure to Toluene - Oral (continued)

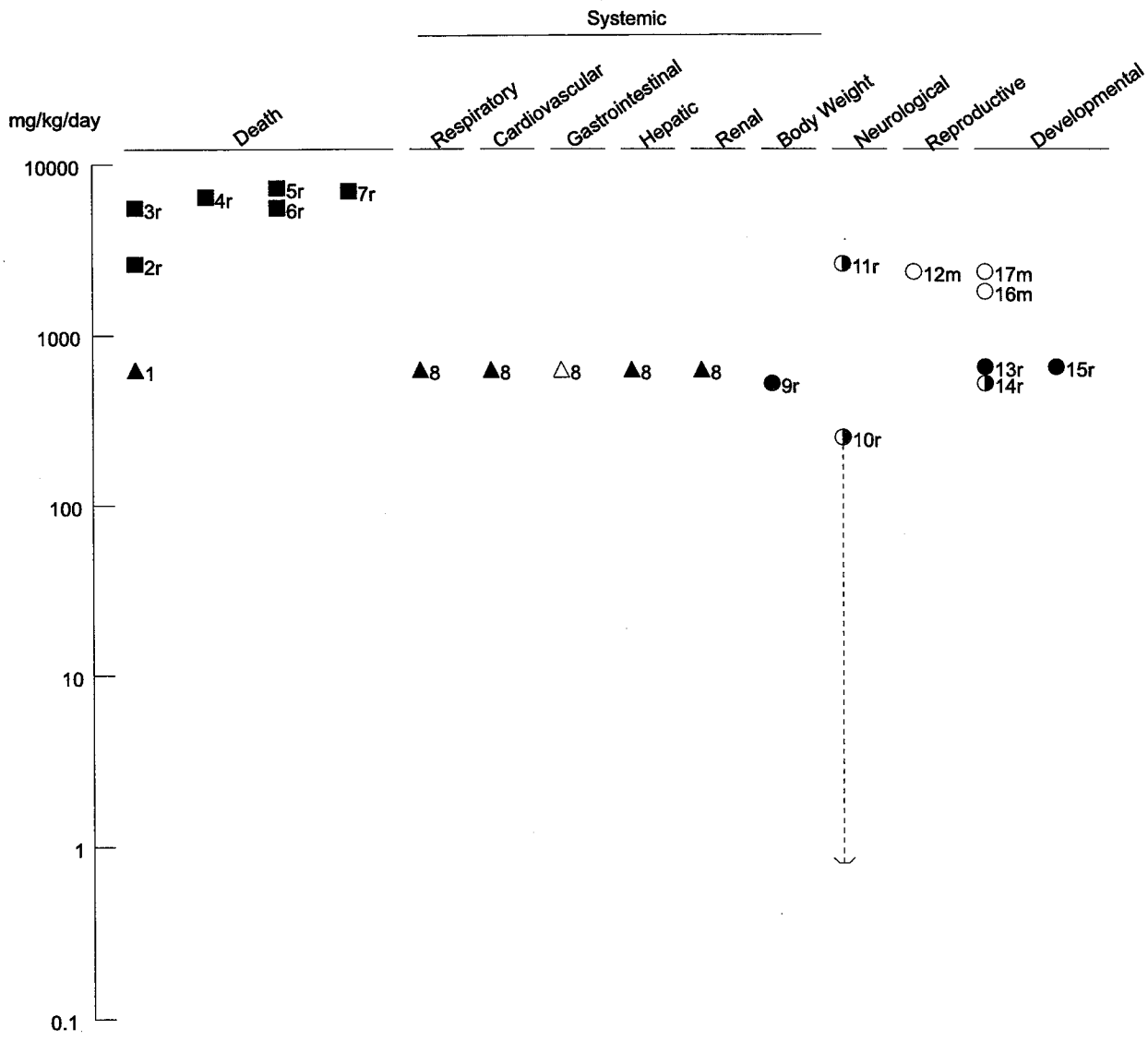
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
Developmental								
31	Mouse (Hybrid)	Gd 0-21 + ppd 0-55 (W)			4	(impaired rotorod performance, motor coordination)		Kostas and Hotchin 1981

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute oral minimal risk level (MRL); dose divided by an uncertainty factor of 300 (3 for use of a minimally adverse LOAEL, 10 for interspecies differences in response, and 10 for human variability), resulting in an MRL of 0.8 mg/kg/day.
[c]Used to derive an acute oral minimal risk level (MRL); dose divided by an uncertainty factor of 300 (3 for use of a minimally adverse LOAEL, 10 for interspecies differences in response, and 10 for human variability), resulting in an MRL of 0.02 mg/kg/day.

Bd = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; FEP = flash evoked potential; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = times

Figure 2-2. Levels of Significant Exposure to Toluene - Oral

Acute (≤14 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◮ LOAEL, Less Serious-Humans	for effects
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	other than
q-Cow	a-Sheep	g-Guinea Pig				Cancer

Figure 2-2. Levels of Significant Exposure to Toluene - Oral (Continued)

Intermediate (15-364 days)

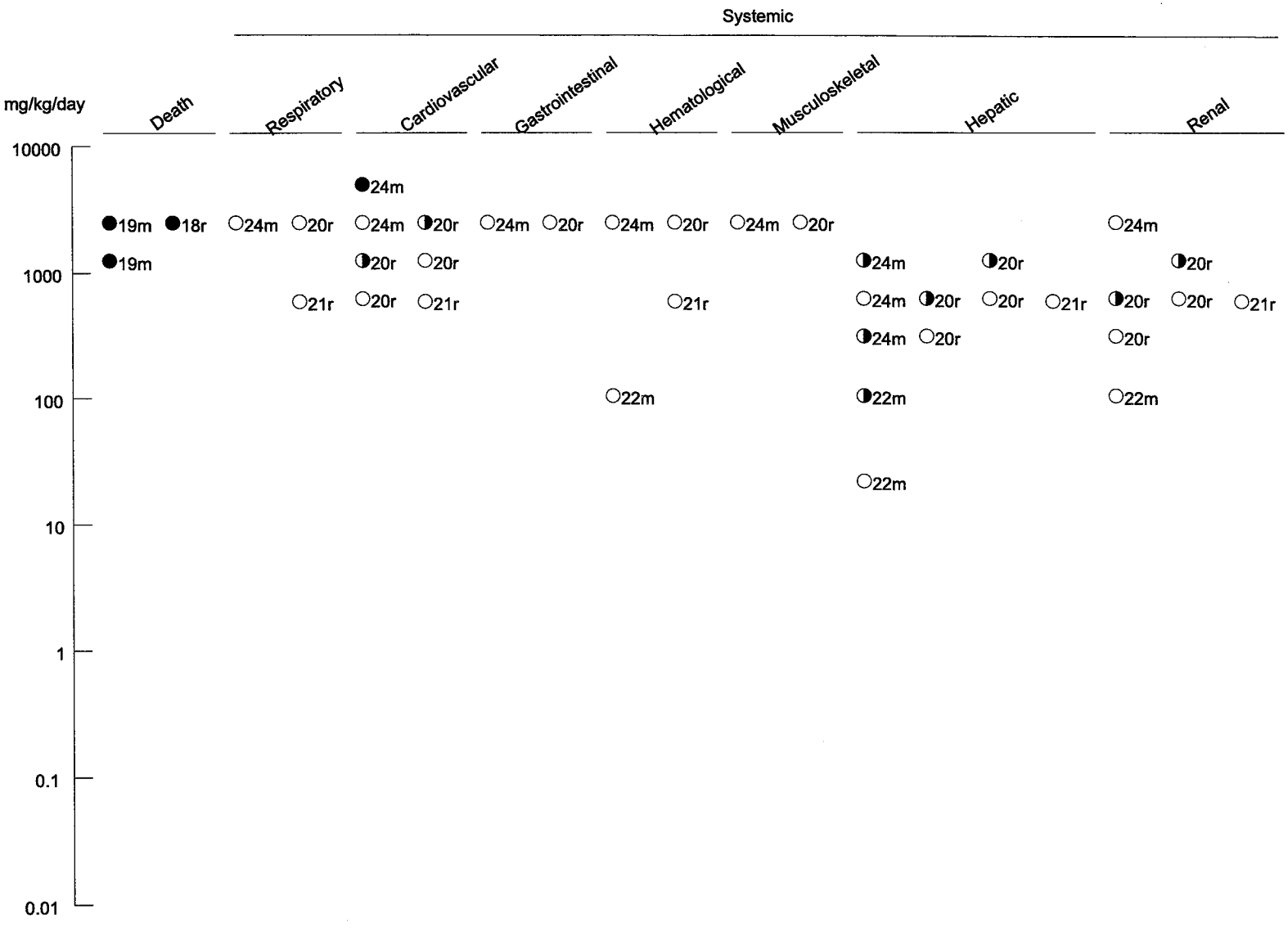
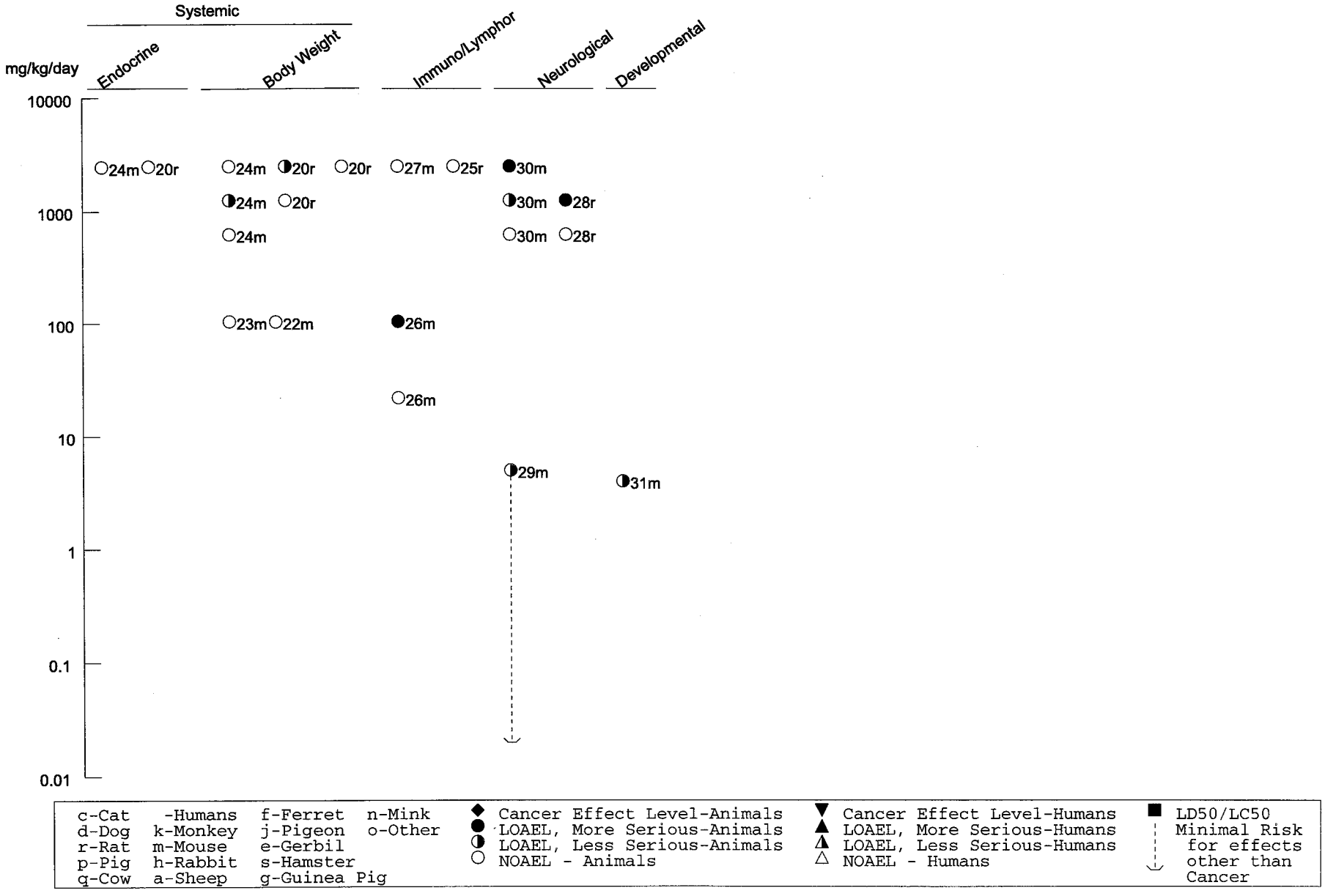


Figure 2-2. Levels of Significant Exposure to Toluene - Oral (Continued)

Intermediate (15-364 days)



Respiratory Effects. Except for lung congestion and hemorrhage in one case report involving lethality (Ameno et al. 1989), no studies were located regarding respiratory effects in humans after oral exposure to toluene.

No respiratory effects were reported in mice or rats after oral exposure to toluene at dosage levels up to 2,500 mg/kg/day for 13 weeks (NTP 1990) or 650 mg/kg/day for 6 months (Wolf et al. 1956).

Cardiovascular Effects. One case study involving lethality in humans reported necrosis of myocardial fibers after oral exposure to 625 mg/kg toluene (Ameno et al. 1989). Severe sinus bradycardia was reported in a man who accidently ingested 30 mL of an organic solvent containing toluene and other chemicals, the patient was drowsy and complained of dizziness and gastric pain (Einav et al. 1997).

Increased relative heart weights were noted in rats exposed to toluene at 1,250 mg/kg/day for 13 weeks and myocardial degeneration was present in mice exposed to 5,000 mg/kg/day (NTP 1990). All of the mice receiving 5,000 mg/kg/day died during the first weeks of exposure. No effects on the weight or gross morphology of the heart were noted in rats receiving 590 mg/kg/day for 6 months (Wolf et al. 1956).

Gastrointestinal Effects. A case report in humans did not reveal gastrointestinal effects even after oral exposure to a lethal dose of toluene (Ameno et al. 1989).

No gastrointestinal effects were reported in mice or rats after oral exposure to toluene at dosage levels up to 2,500 mg/kg/day for 13 weeks (NTP 1990).

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

There were no changes in total erythrocytes in male mice administered 5–105 mg/kg/day toluene in their drinking water for 28 days, although there was a nonsignificant decrease in the concentrations of leukocytes, lymphocytes, and neutrophils (Hsieh et al. 1989). No effect on erythrocyte counts, leukocyte counts, or hemoglobin concentrations resulted in rats exposed to 590 mg/kg/day for 6 months (Wolf et al. 1956). Neither rats nor mice given doses of 312–2,500 mg/kg/day for 13 weeks displayed any compound-related differences in hematological parameters (NTP 1990).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to toluene.

No musculoskeletal effects were reported in mice or rats after oral exposure to toluene at dosage levels up to 2,500 mg/kg/day for 13 weeks (NTP 1990).

Hepatic Effects. The liver of an adult male who died from toluene ingestion (625 mg/kg) was found to be enlarged on autopsy (Ameno et al. 1989).

In mice, there was a significant increase in liver weight after 28 days of ingestion of 105 mg/kg/day toluene in drinking water, but not at doses of 22 mg/kg/day or lower (Hsieh et al. 1989). Relative liver weights increased significantly over control levels in mice administered toluene by gavage for 13 weeks with doses of 312 mg/kg/day and greater in females and 1,250 mg/kg/day and greater in males (NTP 1990). In female rats, the liver weights were increased by exposure to doses of 1,250 mg/kg/day or greater and in male rats by exposure to doses of 625 mg/kg/day or greater. No treatment-related gross or histopathological lesions of the liver were reported (NTP 1990). When rats were exposed for a longer duration, liver weights were not affected and there were no treatment-related lesions in rats that received 590 mg/kg/day toluene by gavage for 6 months (Wolf et al. 1956).

Renal Effects. Data in humans are limited to one case report noting acute tubular necrosis after a lethal exposure to 625 mg/kg (Ameno et al. 1989) and acidosis in another nonlethal case report of thinner consumption (Caravati and Bjerk 1997).

There were no changes in kidney weight for male mice administered doses from 5 to 105 mg/kg/day in drinking water for 28 days (Hsieh et al. 1989), or in female mice given doses of 312–2,500 mg/kg/day by gavage for 13 weeks (NTP 1990). There was a significant decrease in the absolute kidney weight for male mice administered 2,500 mg/kg/day for 13 weeks but no change in the relative kidney weight (NTP 1990). There were significant increases in the relative kidney weights in male rats administered toluene doses of 625 mg/kg/day or greater by gavage for 13 weeks and in females administered doses of 1,250 mg/kg/day (NTP 1990). In addition, lethal exposures of the rats to 5,000 mg/kg/day resulted in hemorrhages of the urinary bladder. No effects on the weight or gross morphology of the kidney were recorded for rats receiving 590 mg/kg/day toluene for months (Wolf et al. 1956).

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to toluene.

Microscopic examination revealed no effects on the adrenal or thyroid glands in rats and mice administered 312–2,500 mg/kg/day toluene by gavage for 13 weeks (NTP 1990).

Dermal Effects. No studies were located regarding dermal effects in humans or animals after oral exposure to toluene.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to toluene.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to toluene.

There were no changes in body weight for male mice administered 5–105 mg/kg/day toluene in their drinking water for 28 days (Hsieh et al. 1989, 1990b). There was also no significant difference in body weights for female rats and female mice given gavage doses of up to 2,500 mg/kg/day for 13 weeks. However, body weights were 16% lower in male mice given 1,250 mg/kg/day and 19% lower in male rats given 2,500 mg/kg/day by gavage for 13 weeks (NTP 1990). Maternal weight gain was 24% lower in rats given 520 mg/kg/day toluene by gavage during gestation days 6–19, compared with control rats (Gospe et al. 1994).

2.2.2.3 Immunological and Lymphoreticular Effects

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

Thymus weights, mixed lymphocyte culture responses, and antibody plaque-forming cell responses were decreased in male mice administered doses of 105 mg/kg/day in their drinking water for 28 days (Hsieh et al. 1989). Mitogen-stimulated lymphocyte proliferation and interleukin-2 immunity were depressed by doses of 22 and 105 mg/kg/day. A dose of 5 mg/kg/day had no effect upon any of these indicators of immune system function. No effects on the histology or weight of the spleen or thymus were reported in rats and mice given gavage doses of up to 2,500 mg/kg/day toluene for 13 weeks (NTP 1990).

The highest NOAEL values and all LOAEL values for each reliable study for immunological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Severe depression of central nervous system function was the probable cause of death for a 51-year-old man who ingested approximately 60 mL (625 mg/kg) of toluene (Ameno et al. 1989). No other studies were located regarding neurological effects in humans after oral exposure to toluene.

Male and female rats exposed to single gavage doses of 2,610, 3,915, or 5,220 mg/kg exhibited changes on a variety of neurological tests (Mehta et al. 1998). Significantly greater increases in motor activities were seen at all doses in both male and female rats on day 1; by day 14 after exposure, there were no significant differences, except for vertical motor activity in female rats was significantly reduced at the 2,620 and 3,915 mg/kg/day doses. A dose-dependent increase in abnormal gait was seen on day 1 for male rats at all doses, while female rats exhibited abnormal gait at 3,915 and 5,220 mg/kg. A dose-dependent increase in lacrimation and salivation was seen on day 1 for both males and females at all doses (Mehta et al. 1998).

Single doses of 250–1,000 mg/kg administered by gavage to male rats caused a decrease in the flash evoked potential wave pattern amplitudes (Dyer et al. 1988). This suggests that toluene may have an effect on the visual system at high doses. The LOAEL of 250 mg/kg/day for the effects of the flash evoked potential waveform was used as the basis for the acute-duration oral MRL (0.8 mg/kg/day) (see Section 2.5 and Appendix A).

Brain levels of norepinephrine (NE), dopamine (DA), serotonin (5-HT), and their respective metabolites, vanillylmandelic acid (VMA), homovanillic acid (HVA), and 5-hydroxyindolacetic acid (5-HIAA) were altered in 6 areas of the brain in male CD-1 mice administered toluene (5–105 mg/kg/day) in their drinking water for a 28-day period (Hsieh et al. 1990b). Significant increases of NE, DA, and 5-HT were present in the hypothalamus at all dose levels. The maximum increase occurred with the 22 mg/kg/day dose and there were lesser increases for both the 5 and 105 mg/kg/day doses. Roughly similar fluctuations were seen in the concentrations of VMA and HVA, which are metabolites of DA and NE and 5-HIAA, a serotonin metabolite. In the corpus striatum, the levels of DA and 5-HT were significantly increased at the two highest doses. The level of VMA was also increased significantly at the same doses. In the medulla oblongata, the concentrations of NE, VMA, and 5-HIAA were significantly increased at

the 22 mg/kg/day dose, but not at the other doses, while the levels of 5-HT were significantly increased at the 22 and 105 mg/kg/day doses. NE concentrations were elevated in the midbrain. The 5 mg/kg/day LOAEL from this study was used as the basis for the intermediate-duration oral MRL (0.02 mg/kg/day) (see Section 2.5 and Appendix A).

Exposure to 1,250 and 2,500 mg/kg/day for 13 weeks resulted in increased relative brain weights in male mice (NTP 1990). Necrosis of the brain was present in rats exposed to 1,250 and 2,500 mg/kg/day, but increases in brain weight were only apparent with the 2,500 mg/kg/day dose (NTP 1990). Clinical signs in rats and mice exposed to 2,500 and 5,000 mg/kg/day included ataxia, hypoactivity, prostration, and tremors. No neurological effects were seen in mice or rats at dose levels of 625 mg/kg/day.

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

2.2.2.5 Reproductive Effects

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

There was no effect on the number of mice producing viable litters following oral administration of 2,350 mg/kg on gestational days 7–14 (Smith 1983). Increased relative testicular weights were reported in male mice exposed to 1,250 and 2,500 mg/kg/day by gavage for 13 weeks. However, no effects on the or weight of the prostate, testes, uterus, or ovaries were observed in rats and female mice exposed to 312–2,500 mg/kg/day (NTP 1990).

The highest NOAEL values and all LOAEL values for reproductive effects in mice following acute duration exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

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

Toluene was not a developmental toxicant when administered orally to pregnant mice during the period of organogenesis at doses of 1,800 or 2,350 mg/kg/day (Seidenberg et al. 1986; Smith 1983). Effects on neurological function were observed in mice exposed from 4 to 106 mg/kg/day toluene through their

dams during gestation and lactation and thereafter through their drinking water. Open-field activity was impaired in mice receiving 106 mg/kg/day toluene when measured on postnatal day 35 (Kostas and Hotchin 1981). There was a distinct effect on rotorod performance during the first 2 of 4 consecutive trials in all exposed mice when measured on postnatal days 45–55. However, the effect on rotorod performance was not dose-related.

Following exposure of pregnant rats to gavage doses of 520 or 650 mg/kg/day toluene in corn oil on gestation days 6–19, fetuses showed significantly reduced body weight, delayed skeletal ossification, smaller brain volumes, and decreases in forebrain myelination per cell compared with controls (Gospe and Zhou 1998; Gospe et al. 1994, 1996). The difference in forebrain myelination was the only difference that remained between exposed and control offspring by postnatal day 21 (Gospe and Zhou 1998).

The highest NOAEL values and all LOAEL values for developmental effects in mice following acute and intermediate duration exposures are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to toluene. Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to toluene.

There is one oral study on the carcinogenic effects of toluene in animals. Toluene was administered at doses of 500 and 800 mg/kg/day to male and female rats for 104 weeks (Maltoni et al. 1997). A nondose-related increase in total malignant tumors in both males and females at all dose levels, in mammary gland tumors in females at the lower dose, in head cancers in males at the higher dose and females at the lower dose, in lymphomas and leukemias in males at the higher dose and females at both doses, were observed (Maltoni et al. 1997). However, the increased incidences were not dose-related and confidence in the study is low.

2.2.3 Dermal Exposure

There are limited data on the effects of dermal exposure to toluene. There are studies describing occupational exposure of humans to toluene (see Section 2.2.1). Toxicokinetic data (Section 2.3) indicate that humans and animals can absorb toluene across the skin. Studies of dermal exposure to toluene in humans and animals are discussed below.

2.2.3.1 Death

No studies were located regarding lethal effects in humans or animals after dermal exposure to toluene.

2.2.3.2 Systemic Effects

Data are available regarding dermal effects in humans and animals after dermal exposure to toluene. No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in humans or animals after dermal exposure to toluene. In addition, there are data on hepatic, renal, and ocular effects in animals after dermal exposure to toluene. The highest NOAEL values and all LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Table 2-3.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to toluene.

Application of 1 mL toluene to the skin of guinea pigs for 16 hours did not alter liver morphology (Kronevi et al. 1979). Because only one dose of toluene was applied and more sensitive indicators of liver toxicity were not monitored, conclusions cannot be derived regarding the hepatic effects of toluene following dermal exposure.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to toluene.

Application of toluene to the skin of guinea pigs for 16 hours did not alter renal morphology (Kronevi et al. 1979). The limitations of this study were discussed in the previous section.

Table 2-3. Levels of Significant Exposure to Toluene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Gn pig (albino)	3 d 3x/d	Dermal		10 ul M (skin irritation)		Anderson et al. 1986
Gn pig (albino)	0.25-16 hr	Hepatic	1 mL			Kronevi et al. 1979
		Renal	1 mL			
		Dermal		1 mL	(karyopyknosis, karyolysis, perinuclear edema, spongiosis, junctional separation, cellular infiltration)	
Rabbit	once	Ocular		0.1mL	(eye irritation)	Hazleton Labs 1962
Rabbit	once	Ocular		0.1 mL	(eye irritation)	M B Research Labs 1975b

Gn Pig = guinea pig; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level

Dermal Effects. In humans, dermal contact with toluene may cause skin damage because it removes skin lipids (EPA 1983a). Workers exposed to mixtures of solvents, of which toluene was generally the major component, reported problems with the skin of their hands (Winchester and Madjar 1986). The specific symptoms associated with the reported skin abnormalities were not reported. Eye irritation in humans occupationally exposed to toluene vapors has also been reported (Meulenbelt et al. 1990). Repeated application of undiluted toluene (amount unstated) to the rabbit ear or shaved skin produced slight to moderate irritation (Wolf et al. 1956). In guinea pigs, continuous contact with toluene resulted in shrinkage and dissolution of the cell nuclei, cellular edema, and cellular infiltration of the dermis (Kronevi et al. 1979). Application of toluene to the skin of guinea pigs, 3 times a day for 3 days, resulted in redness and an increase in epidermal thickness (Anderson et al. 1986). These data suggest that toluene is slightly to moderately irritating to the skin.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to toluene.

Slight irritation of the conjunctival membranes, but no corneal injury, was observed in rabbit eyes following direct application of toluene (Hazleton Laboratories 1962; M B Research Labs 1975; Wolf et al. 1956). Moderately severe injury to the eyes of rabbits following direct application of a 40% solution of toluene has also been reported (Carpenter and Smyth 1946). These data suggest that toluene is slightly to moderately irritating to the eyes.

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

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located for cancer effects in humans after dermal exposure to toluene.

Dermally administered toluene markedly inhibits skin tumorigenesis in the two-stage mouse model utilizing phorbol-12-myristate-13-acetate (PMA) as a promoter (Weiss et al. 1986). The reduction in tumorigenesis was observed in mice initiated with dermal applications of benzo(a)pyrene or 7,12-dimethylbenz(a)anthracene. The pattern of inhibition indicated that the observed effect was not likely to be due to a direct chemical effect on the promoter. The authors speculated that toluene competed for a PMA receptor site, interfered with a biochemical process within the cell membrane, or affected the intracellular cascade between the membrane and the nucleus.

2.3 TOXICOKINETICS

Studies with volunteers and laboratory animals indicate that toluene is readily absorbed from the respiratory and gastrointestinal tracts and, to a lesser extent, through the skin. Animals given toluene orally or by inhalation had high concentrations of toluene in their adipose tissue, brain, and bone marrow, and moderately high concentrations of toluene and its metabolites in liver and kidney. The primary initial steps in toluene metabolism in humans and laboratory animals are side-chain hydroxylation (to form benzyl alcohol) catalyzed predominately by the cytochrome P450 (CYP) isozyme, CYP2E1 (Nakajima and Wang 1994; Nakajima et al. 1991, 1992a, 1992b, 1993, 1997; Tassaneeyakul et al. 1996) followed by oxidation to benzoic acid. Most of the benzoic acid is then conjugated with glycine to form hippuric acid, but a small portion can be conjugated with UDP-glucuronate to form the acyl-glucuronide. Studies with volunteers and human liver microsomes indicate that a very small portion (<1–5%) of absorbed toluene can be converted by CYP1A2, CYP2B2, or CYP2E1 to *ortho*- or *para*-cresol, which are excreted in the urine as sulfate or glucuronate conjugates (Baelum et al. 1993, Nakajima et al. 1997; Tassaneeyakul et al. 1996). In both humans and rats, up to about 75–80% of inhaled toluene that is absorbed can be accounted for as hippuric acid in the urine (Lof et al. 1993; Wang and Nakajima 1992). Much of the remaining toluene is exhaled unchanged. In humans exposed by inhalation, rates of urinary excretion of *ortho*-cresol were about 1,000-fold lower than excretion rates for hippuric acid (Baelum et al. 1993). The excretion of toluene and its metabolites is rapid, with the major portion occurring within 12 hours of exposure.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

In humans exposed to 80 ppm toluene, uptake was rapid as shown by the appearance of toluene (2–5 µmol/L) in the blood within 10–15 minutes of exposure (Hjelm et al. 1988) and by a high correlation between the alveolar and arterial concentrations of toluene both during and after exposure (Carlsson 1982). About 50% of deuterium labeled toluene was absorbed from the lungs in volunteers exposed to 53 ppm for 2 hours during a period of light exercise (Lof et al. 1993). Seven humans exposed to 50 ppm toluene in a closed chamber showed an average retention of 83% of the inspired concentration (Benoit et al. 1985).

Toluene was rapidly absorbed via the lungs of rats; the log concentrations of toluene in the blood and brain were linear functions of the log concentration of toluene in the air (Benignus et al. 1984). In dogs, toluene was found in the arterial and venous blood 2 minutes after the start of exposure (Hobara et al. 1984b).

No information was located regarding possible differences in absorption of inhaled toluene by humans or animals with differences in age.

2.3.1.2 Oral Exposure

Complete gastrointestinal absorption of toluene in human subjects was indicated by monitoring exhaled air for toluene and urine for toluene metabolites (hippuric acid and *ortho*-cresol) following oral administration of toluene as a 2 mg/min infusion for 3 hours through a feeding tube into the stomach (Baelum et al. 1993). Complete absorption of orally administered toluene has also been observed in rats, but oral absorption rates appear to be slower than pulmonary absorption (Pyykko et al. 1977). In this rat study, maximum blood concentrations were observed 1.5–3 hours after administration, whereas maximum blood levels following inhalation were reached in 15–30 minutes.

Ingestion of soil contaminated with toluene can be a concern at hazardous waste sites. Binding to soil does not prevent absorption. The time course for absorption of toluene mixed with sandy soil or clay soil was increased when compared to the time course for pure toluene, but the total amount absorbed was the same based on the area under the blood toluene concentration curve (Turkall et al. 1991).

Studies with brush border membrane vesicles isolated from rat intestines and exposed to toluene indicate that toluene absorption occurs through the lipophilic matrix of the membrane (Alcorn et al. 1991). The removal of proteins from the membrane surface had no effect upon the toluene partition coefficient, but factors affecting the nonesterified membrane fatty acids reduced absorption. In this same *in vitro* study of membrane partitioning, vesicles harvested from the proximal, middle, and distal intestinal segments showed no differences, indicating that concentration and surface area, rather than membrane structure, are the factors determining the amount of toluene absorbed from each portion of the small intestines. Since toluene absorption occurs through the lipid matrix of the membrane, absorption can occur through the mouth and stomach, as well as the small intestines. The amount of toluene absorbed from each organ of the gastrointestinal tract will depend on residence time, absorptive surface area, and partitioning between membrane lipids and lipids in the gastrointestinal tract.

No information was located regarding possible differences in absorption of ingested toluene by humans or animals with differences in age.

2.3.1.3 Dermal Exposure

Toluene is absorbed through human skin slowly (Dutkiewicz and Tyras 1968). The rate of absorption of toluene in human forearm skin was found to range from 14 to 23 mg/cm^2/hour. Based on these estimates, Brown et al. (1984) calculated that bathing in water containing 0.005–0.5 mg toluene/L (15 minutes/day) would result in absorbed dermal dose ranges of 0.0002–0.02 mg/kg/day for a 70-kg adult and 0.0004–0.04 mg/kg/day for a 10.5-kg infant.

Soaking the skin of 2 volunteers with toluene for 5 minutes resulted in a maximum concentration of toluene in blood of 5.4 µmol/L (Aitio et al. 1984). Individual differences were marked, and dramatic changes in blood concentrations were observed over short periods of time. Similar individual differences and highly variable results were reported by Sato and Nakajima (1978) in a study using five volunteers.

Monster et al. (1993) investigated dermal absorption of toluene in 6 rotogravure printing workers. The workers washed their hands with toluene for 5 minutes, and alveolar air samples were collected up to 24 hours after exposure. The concentrations measured the next morning in exhaled air ranged between 0.5 and 10 mg/m^3, clearly demonstrating dermal absorption of toluene.

Toluene in aqueous solution and neat toluene were absorbed through the skin of rats (Morgan et al. 1991). Three solution strengths (0.162, 0.333, and 0.448 mg/L) were tested. Although the blood toluene levels for each strength were near the analytical detection limits, the results of this study indicate that toluene absorption was significant, since only 1% of the body surface was exposed.

Dermal absorption also occurs when animals are exposed to toluene vapors. In nude mice exposure to 300, 1,000, or 3,000 ppm toluene under conditions where there was no respiratory intake of toluene, led to a dose-related and duration-related increase in whole body toluene levels (Tsuruta 1989). The calculated skin absorption coefficient was 1.24 cm/hour. The skin absorption rate for the 300 ppm concentration was 0.0009 mg/cm^2/hour; for the 1,000 ppm concentration, it was 0.0046 mg/cm^2/hour; and for the 3,000 ppm concentration, it was 0.0144 mg/cm^2/hour. Exposure of guinea pigs to an unspecified concentration of toluene for 1 minute, with the skin wiped dry and 1 minute exposures continuing every 30 minutes, for 4 hours, resulted in lower levels of toluene absorption than with continuous exposure for 4 hours (Boman et al. 1995).

No information was located regarding possible differences in absorption of dermally applied toluene by humans or animals with differences in age.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

There is a positive correlation between the levels of toluene in alveolar air and the levels in blood in both humans and animals (Hjelm et al. 1988; Lof et al. 1990; Ovrum et al. 1978). With an exposure in humans of 80 ppm toluene for 4 hours, toluene levels in the blood reached a plateau of 6–7 µmol/L at approximately 2 hours (Hjelm et al. 1988; Lof et al. 1990). In humans, the toluene is distributed between the plasma and red blood cells at approximately a 1:1 ratio according to *in vitro* data; in rats, the ratio is 1:2 based on *in vivo* data (Lam et al. 1990). In the red blood cells, the toluene appears to be associated with the hemoglobin rather than the cell membrane. It is hypothesized that toluene interacts with the hydrophobic core of the heme protein. The interaction of the toluene with the red blood cell increases the amount of toluene that can be accommodated by the aqueous blood medium and facilitates transport of toluene to all areas of the body (including the brain) at a rate that is greater than if toluene was transported only in the plasma.

Autopsies of toluene-exposed humans indicate that absorbed toluene is distributed to lipid-rich and highly vascular tissues such as the brain. For example, toluene levels in the brain and liver of a 16-year-old male who died following an episode of glue sniffing were 297 and 89 µg/mg, respectively (Paterson and Sarvesvaran 1983). Concentrations in the blood were 20.6 µg/mL of toluene and 3.0 µg/mL of acetone. In a man who died following a fall while exposed to toluene during painting, tissue levels of toluene in blood, lung, liver, and brain were 48, 35, 65, and 80 µg/g, respectively (Takeichi et al. 1986).

Within the human brain, toluene has a greater affinity for areas of the brain that contain lipid-rich white matter, such as the brain stem, rather than the areas with larger amounts of gray matter (Ameno et al. 1992). The hippocampus and cerebellum had lower brain: blood toluene ratios than the spinal cord, midbrain, medulla oblongata, and pons. The brain stem controls many involuntary aspects of cardiac, respiratory, and vasomotor function.

Concentrations of toluene in subcutaneous adipose tissue of male subjects exposed during rest or physical exercise to 300 mg/m^3 of toluene were determined (Carlsson and Ljungquist 1982). After exposure at rest for 2 hours, the mean concentration of toluene in adipose tissue was 0.7 mg/kg. The corresponding value after 2 hours of work was 9.9 mg/kg. Linear regression analysis indicated that toluene concentrations in adipose tissue were lower in subjects with large amounts of body fat.

The human data are supported by autoradiography studies using mice. Immediately after inhalation, a high level of radioactivity was found in the body fat, bone marrow, spinal nerves, spinal cord and white matter of the brain of exposed mice (Bergman 1979). Radioactivity was also observed in the blood, kidney, and liver at lower levels. Autoradiography of mice sacrificed immediately after the cessation of exposure revealed a very high concentration of nonvolatile radioactivity in the kidney, particularly the medullary region. Nonvolatile radiation found in the liver and kidney suggests rapid formation and excretion of toluene metabolites.

A one-compartment model was developed for blood and whole-brain toluene levels based on data from rats exposed to 575 ppm toluene for up to 240 minutes (Benignus et al. 1981). Estimated saturation asymptotes were 10.5 ppm for venous blood and 18.0 ppm for brain, respectively. Blood and brain levels achieved 95% of their estimated asymptotes in 53 and 58 minutes, respectively. The distribution half-life for a 30-minute exposure of rats to 2,000 ppm toluene was 0.34 hours, while that for exposure to 10,000 ppm was 0.6 hours (Ameno et al. 1992).

Toluene was rapidly distributed to the tissues in rats after 1, 2, or 3 days of exposure to 100 ppm for 12 hours per day (Zahlsen et al. 1992). Homeostasis was attained in 1 day for the kidney, brain, and liver, whereas toluene concentrations continued to increase in perirenal fat deposits. Once exposures ceased, toluene concentrations declined within 12 hours to near baseline levels for all tissues except in fat. The toluene in rat brains was distributed to the brain stem and midbrain (Ameno et al. 1992), a distribution that parallels that observed in humans and mice (Ameno et al. 1992; Bergman 1979). These regions have a high concentration of white matter.

Toluene distribution to several tissues was followed in dogs exposed through inhalation of 30,000 ppm toluene from a plastic bag for 10 minutes. The toluene level in the arterial blood was 129±54.8 µg/mL while that in the venous blood was 112±48.5 µg/mL. The liver and brain contained roughly equivalent concentrations of toluene (184 and 191 µg/g), while the toluene in the kidneys was 99 µg/g (Ikeda et al. 1990).

Distribution of toluene (assayed by autoradiography and tissue concentrations of radioactivity) in pregnant mice was also characterized by preferential uptake in maternal lipid-rich tissues (brain and fat) immediately after 10-minute inhalation exposures to ^{14}C-labeled toluene at approximately 2,000 ppm (Ghantous and Danielsson 1986). It was thought that toluene, due to its high lipid solubility and low molecular weight, might easily transfer across the placenta, but concentrations of radioactivity in fetal tissues were only about 4% of concentrations in maternal brain and adipose tissue immediately after exposure, and rapidly decreased within 4 hours of cessation of exposure. These results suggest that absorbed toluene is preferentially distributed to maternal adipose tissues in pregnant mice and that distribution to the developing fetus is limited with short-term exposure to the relatively high (compared with occupational exposures) concentration of 2,000 ppm. This concentration, however, is low compared with concentrations experienced by toluene abusers (4,000–12,000 ppm as cited by Gospe et al. 1994). Ghantous and Danielsson (1986) suggested that the lower lipid content in fetal tissue compared with maternal tissue could explain the low uptake of toluene into fetal tissue.

No studies were located that examined *in vivo* distribution of toluene into breast milk in humans or animals. Although breast milk is high in lipid content, it is unknown if there may be preferential uptake of toluene into other maternal lipid-rich tissues. A published estimate of the human milk/blood partition coefficient for toluene, 2.68, was lower than estimates of coefficients for partitioning of toluene between other tissues and human blood, including liver or highly perfused tissues/blood (4.91) and fat/blood (60.01) (Fisher et al. 1997). Transfer from blood to a tissue, however, is also dependent on the rate of

perfusion of the tissue with blood. Fisher et al. (1997) used these partition coefficient values in a physiologically-based pharmacokinetic (PBPK) model designed to predict transfer of volatile chemicals into breast milk, but human or animal pharmacokinetic data for lactational transfer of toluene were not available to validate or modify the model.

Coexposure of rats to xylene increased the concentrations of toluene in the blood and brain in the 19 hours after exposure as compared to exposure to toluene alone (Tardif et al. 1992). This was, apparently, the result of suppressed toluene metabolism because of competition between toluene and xylene for active sites on enzymes responsible for metabolizing both compounds. Pulmonary excretion of toluene was also decreased when exposure to both compounds occurred. As a result, the half-lives for both toluene and xylene were increased.

Blood and brain toluene levels in rats exposed to 2000 or 4000 ppm for 4 hours during daylight were significantly higher at the end of exposure and 40 minutes after the cessation of exposure than in animals exposed in the dark (Harabuchi et al. 1993). This suggests that circadian rhythms may have an influence on toluene absorption, distribution, and excretion.

2.3.2.2 Oral Exposure

In one human who died 30 minutes after ingestion of 625 mg/kg toluene, the liver was found to have the highest concentration of toluene (433.5 µg/g) followed by the pancreas (88.2 µg/g), brain (85.3 µg/g), heart (62.6 µg/g), blood (27.6 µg/g), body fat (12.2 µg/g), and cerebrospinal fluid (11.1 µg/g) (Ameno et al. 1989). The short interval between toluene exposure and death limited the distribution of the toluene to the peripheral body tissues.

When rats were orally exposed to 400 mg/kg toluene, the peak concentration in the blood occurred 1.5 hours after exposure (Ameno et al. 1992). In the brain, the highest brain: blood toluene ratios were found in the pons and caudate-putamen, as opposed to the hippocampus (Ameno et al. 1992). Toluene distribution in the brain was similar with inhalation and oral exposure (Ameno et al. 1992).

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of toluene in humans or animals after dermal exposure.

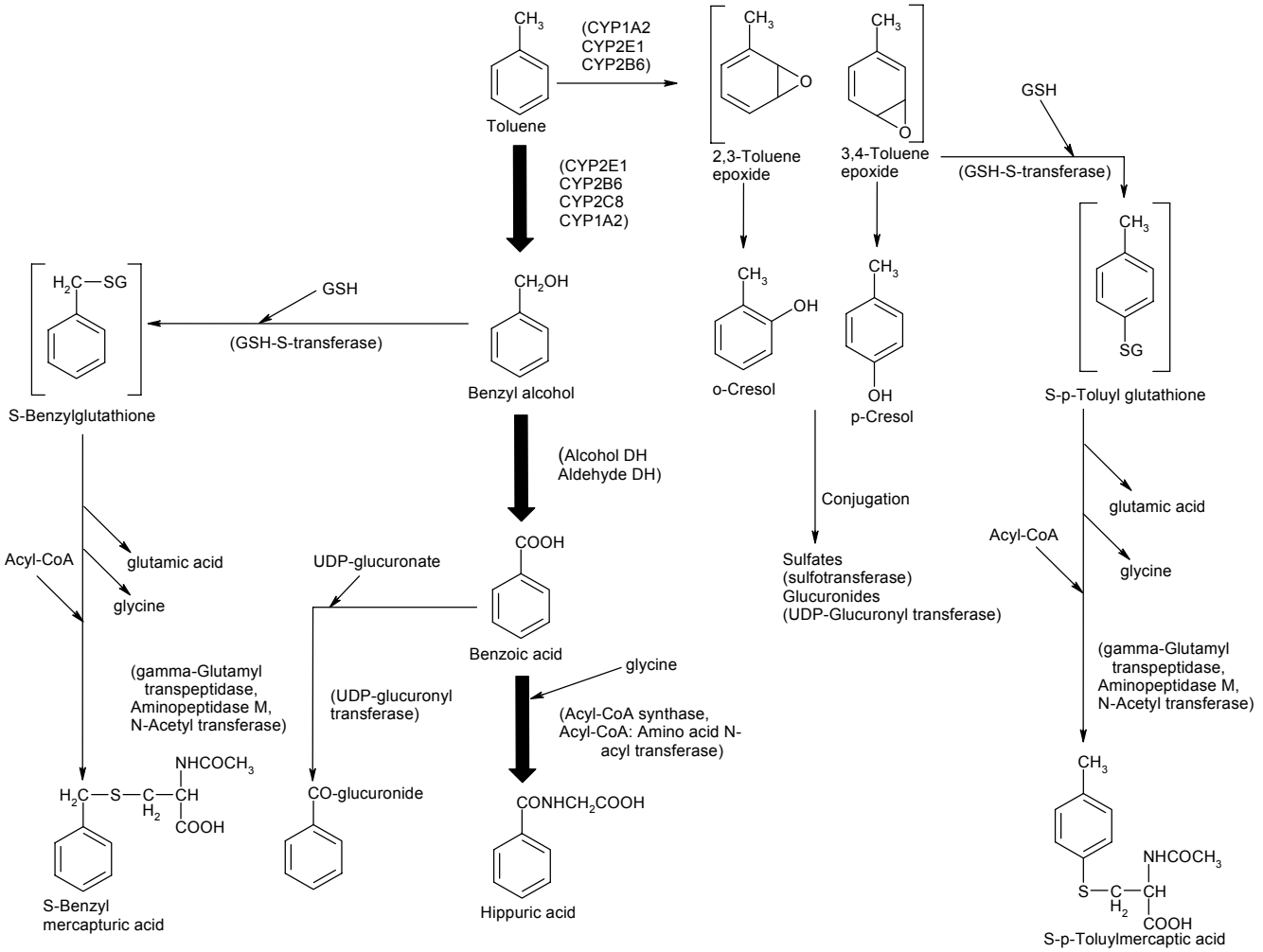
2.3.3 Metabolism

Studies of urinary metabolites in toluene-exposed humans (Andersen et al. 1983; Angerer 1979; Angerer et al. 1998a; Baelum et al. 1987, 1993; Dossing et al. 1983b; Inoue et al. 1986; Jonai and Sato 1988; Kawai et al. 1992a, 1992b, 1993, 1996; Lof et al. 1990, 1993; Maestri et al. 1997; Ng et al. 1990) and rats (Bray et al. 1949; Van Doorn et al. 1980; Wang and Nakajima 1992) have identified hippuric acid (the glycine conjugate of benzoic acid) as the major urinary metabolite of toluene. Minor urinary metabolites (in approximate order of decreasing abundance) include: the glucuronyl conjugate of benzoic acid; sulfate and glucuronide conjugates of *ortho*- and *para*-cresol; S-benzylmercapturic acid; and S-*p*-toluylmercapturic acid. Based on these results and the results from *in vitro* studies, including recent studies with human and rat liver microsomes (Nakajima and Wang 1994; Nakajima et al. 1991,1992a, 1992b, 1993, 1997; Tassaneeyakul et al. 1996), a scheme for toluene metabolism in humans and animals is presented in Figure 2-3.

The initial steps are methyl and ring hydroxylations that are catalyzed by cytochrome P450 (CYP) isozymes. Methyl hydroxylation to form benzyl alcohol was the predominant first step in human (Nakajima et al. 1997; Tassaneeyakul et al. 1996) and rat (Nakajima et al. 1991, 1992a, 1992b, 1993) liver microsomes. Ring hydoxylation to form *ortho*- or *para*-cresols in these studies usually represented less than 5% of total metabolite formation.

Results from *in vitro* studies indicate that CYP2E1 is the most active CYP isozyme in forming benzyl alcohol and CYP1A2 is the most active in forming *ortho*- and *para*-cresols. Using monoclonal antibodies to CYP isozymes as *in vitro* metabolic inhibitors in rat microsome preparations, Nakajima et al. (1991) demonstrated that CYP2E1 (at low toluene concentrations) contributes to the formation of benzyl alcohol and *para*-cresol, CYP1A1/2 contributes to *ortho*- and *para*-cresol formation, and CYP2B1/2 and CYP2C11/6 (at higher toluene concentrations) contribute to the formation of benzyl alcohol and *ortho*- and *para*-cresol. Biphasic enzyme kinetics for the formation of benzyl alcohol from toluene were observed in human liver microsomes, supporting the concept that at least two isozymes with differing affinity for toluene can catalyze benzyl alcohol formation (Tassaneeyakul et al. 1996). The high-affinity component in human liver microsomes was markedly inhibited (about 90% inhibition) by 50 μM diethyldithiocarbamate, an inhibitor of CYP2E1, whereas inhibitors of other CYP isozymes produced generally less than 10% inhibition of the high affinity component (Tassaneeyakul et al. 1996). Other inhibitors tested (and the CYP forms that they are expected to inhibit) were: furafylline (CYP1A2), coumarin (CYP2A6), mephenytoin (CYP2C19), quinidine (CYP2D6), sulfaphenazole (CYP2D6), and

Figure 2-3. Scheme for Toluene Metabolism in Humans and Animals



Proposed enzymes are noted in parentheses.

Sources: Angerer et al. 1998a; IARC 1999; Nakajima and Wang 1994; Nakajima et al. 1997; Tassaneeyakul et al. 1996

CoA = coenzyme A; CYP = cytochrome P-450; DH = dehydrogenase; GSH = glutathione; UPD = uridine 5'-diphosphate

troleandomycin (CYP3A) (Tassaneeyakul et al. 1996). Using microsomes from cells in which cDNAs for eleven different human CYP isozymes were expressed, Nakajima et al. (1997) demonstrated that CYP2E1 was the most active in forming benzyl alcohol, followed in order by CYP2B6, CYP2C8, CYP1A2, and CYP1A1. The activities of CYP2A6, CYP2C9, CYP2D6, CYP3A3, CYP3A4, and CYP3A5 in metabolizing toluene were negligible. CYP1A2 also was active in forming *ortho*- and *para*-cresol (22 and 35% of total metabolites) and CYP2E1 and CYP2B6 catalyzed the formation of *para*-cresol (11–12% of total metabolites) (Nakajima et al. 1997).

Benzyl alcohol is thought to be converted to benzoic acid in two steps by alcohol dehydrogenase and aldehyde dehydrogenase (see Figure 2-3). Conjugation with glycine to form hippuric acid can represent 83–94% of urinary metabolites of toluene in rats (Nakajima and Wang 1994). Hippuric acid formation from benzoic acid (a common component of the diet) is catalyzed by acyl-CoA synthetase and acyl-CoA: amino acid N-acyltransferase. Conjugation of benzoic acid with glucuronic acid to form benzoyl glucuronide is catalyzed by UDP-glucuronyl transferase and can account for 3–9% of urinary metabolites in rats (Nakajima and Wang 1994).

The 2,3- and 3,4-epoxide intermediates, precursors of *ortho*- and *para*-cresol, are thought to be oxidation products of the catalytic actions of CYP1A2, CYP2E1, and CYP2B6 (Nakajima et al. 1997). *Ortho*- and *para*-cresol and their conjugates have been reported to account for 0.5–1.1% and 2.5–14.2%, respectively, of urinary metabolites in rats (Nakajima and Wang 1994). S-benzyl mercapturic acid, a minor urinary metabolite identified in humans, is thought to be formed via conjugation of benzyl alcohol with glutathione (catalyzed by glutathione-S-transferases), followed by the concerted catalytic actions of γ-glutamyltranspeptidase, amino peptidase M, and N-acetyltransferase to release glutamic acid and glycine and add an acetyl group (Angerer et al. 1998a) (see Figure 2-3). The formation of another minor human urinary metabolite, S-*p*-toluylmercapturic acid, is thought to proceed by a similar series of reactions from the proposed intermediate, 3,4-toluene epoxide (Angerer et al. 1998a).

The liver is expected to be the prime site of toluene metabolism, based on the high concentration of CYP isozymes in the liver relative to other tissues. For example, levels of CYP2E1 in human lung microsomes were 10.5% of liver activities (Wheeler et al. 1992). Studies with rats indicate that toluene exposure causes changes in CYP-associated enzyme activities and CYP isozymes themselves in the liver (see Nakajima and Wang 1994 for review). For example, single 6-hour exposures to toluene induced hepatic CYP2E1 levels and associated nitrosodimethylamine demethylase activities (at concentrations $1,000 ppm), induced CYP2B1/2 and CYP3A1/2 levels (at concentrations >2,000 ppm), decreased

CYP2C11/6 levels (at 4,000 ppm), and did not change CYP1A1/2 levels (Wang et al. 1993). Other rat experiments involving longer durations of exposure and potentially higher dose levels have consistently observed induction of hepatic activities of aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin O-deethylase (EROD), activities associated with CYP1A1/2 (see Nakajima and Wang 1994). Rats given single intraperitoneal injections of 5 mmol toluene/kg showed induction of ethoxycoumarin O-deethylase (ECOD) and EROD activities in liver, but no induction was apparent in lung or kidney tissues (Pyykko et al. 1987). Exposure of rats to 375 ppm toluene, 6 hours/day for up to 5 days or 125 ppm for 6 hours did not significantly change activities of AHH, EROD, or benzyloxyresorufin (BROD) in liver microsomes compared with activities in nonexposed controls, but significantly decreased activities of AHH (by up to about 50%), BROD (by 30–70%), and 2-aminofluorene N-hydroxylase (by up to about 50%) in lung microsomes without altering EROD activities (Furman et al. 1998). The results from these rat studies suggest that toluene at exposure concentrations $1,000 ppm, but not at lower concentrations, induces hepatic CYP enzymes involved in its own metabolism and metabolism of other xenobiotics, and that exposure to 125 or 375 ppm may cause a decrease in pulmonary activities of certain CYP mixed function oxidases. Consistent with the idea of no CYP induction with low-level exposure is the report that workers exposed to 100 ppm toluene did not display increased ability to clear antipyrine (Dossing et al. 1983c).

Levels of CYP isozymes in rat fetal livers are very low, but increase rapidly after birth (Nakajima and Wang 1994). By 10 days after birth, rats of both sexes are capable of responding to toluene exposure by inducing hepatic CYP-associated enzyme activities (Pyykko 1983b). Comparison of rates of metabolism in liver microsomes from male and female rats at 3 weeks (immature) and 18 weeks of age (mature) and in pregnant female rats on gestations days 10 and 21 indicate that age, gender, and pregnancy can influence rates of hepatic toluene metabolism and induction of CYP isozymes (Nakajima et al. 1992b). Rates (on a mg protein basis) of high-affinity toluene metabolism were not statistically significantly different between immature and mature male rats, but rates of low-affinity toluene metabolism were four-fold higher in mature rats compared with immature rats (Nakajima et al. 1992b). In contrast, rates of high-affinity toluene metabolism were lower in mature than in immature female rats, but rates of low-affinity toluene metabolism were not statistically different between immature and mature female rats. Rates of high- and low-affinity toluene metabolism were significantly lower in pregnant rats compared with nonpregnant rats.

Given the lack or low levels of several CYP isozymes in the developing human fetus (Leeder and Kearns 1997), it is expected that the capacity for metabolic detoxification of toluene is low in the developing

fetus. Rat studies indicate that levels of CYP isozymes involved in toluene metabolism, however, are rapidly increased following birth, and suggest that capabilities to carry out Phase I toluene metabolism at low exposure levels during neonatal periods may exceed those at sexual maturity and pregnancy (Nakajima et al. 1992b). CYP2E1, one of the principal CYP isozymes involved in the major toluene pathway (Nakajima et al. 1997; Tassaneeyakul et al. 1996), is reported to be expressed several hours after birth in humans and continues to increase during the first year of life (Vieira et al. 1996). Phase II enzymes involved in toluene metabolism (e.g., N-acetyl transferases, UDP-glucuronyl transferases, and sulfotransferases) also show changes during human neonatal development with adult activities reported to be present by 1–3 years of age (Leeder and Kearns 1997). Although no studies were located directly comparing toluene metabolic capacity in children and adults, the limited available information suggest that children past early neonatal periods may be equally able as adults in metabolically disposing of toluene at low exposure levels expected to be found in the general environment or at sites adjacent to waste sites.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Studies with humans and laboratory animals indicate that following acute periods of inhalation exposure to toluene, absorbed toluene is excreted predominately in the urine as metabolites (hippuric acid, benzoyl glucuronide, *ortho*- and *para*-cresol and their sulfate and glucuronide conjugates, S-benzyl mercapturic acid, and S-*p*-toluyl mercapturic acid, as discussed in Section 2.3.3) and, to a lesser extent, as non-metabolized toluene in exhaled air (Lof et al. 1993; Ogata 1984; Tardif et al. 1998). For example, following a 2-hour exposure with light physical exercise to deuterium-labeled toluene at a concentration of 200 mg/m^3 (53 ppm), an average 78% of retained label was excreted as urinary hippuric acid within 20 hours by a group of nine volunteers (Lof et al. 1993). A significant portion of absorbed toluene in this and other studies has been estimated to be exhaled as nonmetabolized toluene (7–20% of absorbed toluene) (Carlsson 1982; Leung and Paustenbach 1988; Lof et al. 1993).

Analyses of kinetic data for toluene concentrations in blood, exhaled breath, or adipose tissue following inhalation exposure of humans (Leung and Paustenbach 1988; Lof et al. 1993; Pellizzari et al. 1992; Pierce et al. 1996, 1999) and rats (Rees et al. 1985) indicate that most absorbed toluene is rapidly eliminated from the body and that a smaller portion (that which gets into adipose tissues) is slowly eliminated. Using three-phase exponential mathematical models to describe curves of human blood

concentration as a function of time up to 3–5 hours after 2-hour exposures to 100 or 53 ppm toluene, calculated half-lives (the time to decrease the amount in the phase by one-half) were 1.5 and 3 minutes for the initial phase, 26 and 40 minutes for the second phase, and 3.7 and 12.3 hours for the final phase (Lof et al. 1993; Sato et al. 1974). Elimination half-lives ranged from about 12 to 65 hours (0.5 to 2.7 days) in subcutaneous adipose tissue samples taken from 12 subjects at several times within 8 days of cessation of exposure to about 80 ppm toluene for four consecutive 30-minute periods (Carlsson and Ljungquist 1982). Increasing elimination half-lives were significantly correlated with increasing amounts of body fat (Carlsson and Ljungquist 1982). Using PBPK models, mean terminal half-lives of about 30–38 hours were calculated for changes in blood toluene concentrations between 50 and 100 hours after cessation of 2-hour inhalation exposures of male subjects to 50 ppm $^{1}H_{8}$-toluene and 50 ppm $^{2}H_{8}$-toluene (Pierce et al. 1996, 1999). During this terminal phase of disposition, >95% of toluene is expected to be in adipose tissue and the release of toluene from adipose tissues has been proposed to be the rate-limiting step (Pierce et al. 1999). In studies with rats exposed for 2 hours to 1,000, 1,780, or 3,000 ppm toluene, two-phase exponential models were used to calculate average elimination half-lives of approximately 6 and 90 minutes, but blood toluene concentrations were monitored in this study for no more than 2 hours following exposure (Rees et al. 1985).

Investigators have reported a correlation between occupational exposure to toluene and urinary excretion of hippuric acid, *o*-cresol, and *p*-cresol (De Rosa et al. 1985, 1987; Foo et al. 1991; Kono et al. 1985; Lof et al. 1993; Ogata 1984). However, experts caution that there are individual differences in the amounts of these excreted metabolites, and monitoring of urinary excretion of metabolites can only serve as a qualitative indication of exposure to toluene (Andersen et al. 1983; Baelum et al. 1987; Hasegawa et al. 1983; Kawai et al. 1996; Nise 1992). When volunteers were exposed to 50 ppm deuterium-labeled toluene plus 50 ppm nonlabeled toluene, there was very little variation of labeled hippuric acid excretion between subjects (Lof et al. 1993). After 20 hours, 78% of the absorbed labeled toluene was excreted as labeled hippuric acid. However, unlabeled hippuric acid excretion varied widely between subjects and the total amount of hippuric acid excreted was about 4 times greater than what would have been generated by toluene exposure alone. This indicates that there are a number of hippuric acid precursors present in the environment (e.g., benzoic acid in food) and exposure to these compounds varies, making hippuric acid excretion a poor indicator of toluene exposure.

Studies of workers exposed to low levels of airborne toluene (TWA concentrations below 50 ppm) indicated that correlation coefficients between end-of-shift levels of *ortho*-cresol and hippuric acid in urine and toluene concentrations in breathing zone air, although statistically significant, were not above

0.7, indicating a fair amount of variation not explained by toluene air concentrations (Kawai et al. 1996; Nise 1992). In a study of 17 workers exposed to 8-hour TWA breathing zone toluene concentrations ranging from about 5 to 70 ppm, end-of-shift levels of S-benzylmercapturic acid in urine were correlated with toluene concentrations with a coefficient of 0.74 (Maestri et al. 1997). In addition to the individual differences for urinary metabolites, possible ethnic differences in the excretion of hippuric acid and o-cresol have also been reported in Chinese, Turkish, and Japanese solvent workers (Inoue et al. 1986). Significant differences in *o*- and *p*-cresol/hippuric acid ratios in the urine were also seen in four different strains of rats exposed to toluene (Inoue et al. 1984).

The American Conference of Governmental Industrial Hygienists (ACGIH 1999) recommends using a combination of three biological exposure indices to assess exposure of workers to toluene in the workplace: *ortho*-cresol and hippuric acid levels in urine at the end of a workshift and toluene levels in blood immediately prior to the last shift of a workweek. Angerer et al. (1998a) proposed that S-*p*-toluylmercapturic acid levels in urine may also be useful as a biological indicator of toluene exposure.

2.3.4.2 Oral Exposure

Following oral administration of toluene to eight male subjects by a 2 mg/minute infusion for 3 hours through a feeding tube into the stomach, nonmetabolized toluene was detected in alveolar air samples for up to 4 hours after cessation of exposure and rates of urinary excretion of hippuric acid and *ortho*-cresol were elevated compared with values under nonexposed conditions (Baelum et al. 1993). A 6 mg/minute infusion for 30 minutes did not change the rates of urinary excretion of hippuric acid and *ortho*-cresol, but increased, by four-fold, the area-under-the-curve (AUC) for alveolar toluene concentration compared with the values for the 2-mg/minute exposure protocol. Accompanying the 2-mg/minute exposure protocol with oral doses of ethanol (0.32 g/kg, corresponding to two alcoholic drinks) decreased hippuric acid urinary excretion and dramatically increased the AUC for alveolar toluene concentration (by about 850-fold in one experiment and 56-fold in another). These data indicate that orally administered toluene is eliminated similarly to inhaled toluene, (i.e., by urinary excretion of metabolites and exhalation of nonmetabolized toluene), and that ingestion of ethanol can have a dramatic effect on metabolism and subsequent elimination of toluene. The results are consistent with other studies showing that ethanol inhibits the major toluene metabolic pathway, side-chain oxidation (Dossing et al. 1984; Wallen et al. 1984).

No other studies were located regarding the excretion of toluene in humans or animals after oral exposure.

2.3.4.3 Dermal Exposure

Following a 5-minute episode of hand-washing in toluene while wearing an airstream helmet to limit inhalation exposure, toluene concentrations in exhaled air from human subjects peaked at about 1 ppm at 22 minutes and declined to about 0.03 ppm at 24 hours (Monster et al. 1993). The results from this study indicate that dermally absorbed toluene can be eliminated as the parent compound in exhaled breath, but provide no information concerning the possible urinary excretion of metabolites.

No other studies were located regarding elimination of toluene following dermal exposure.

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

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (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.

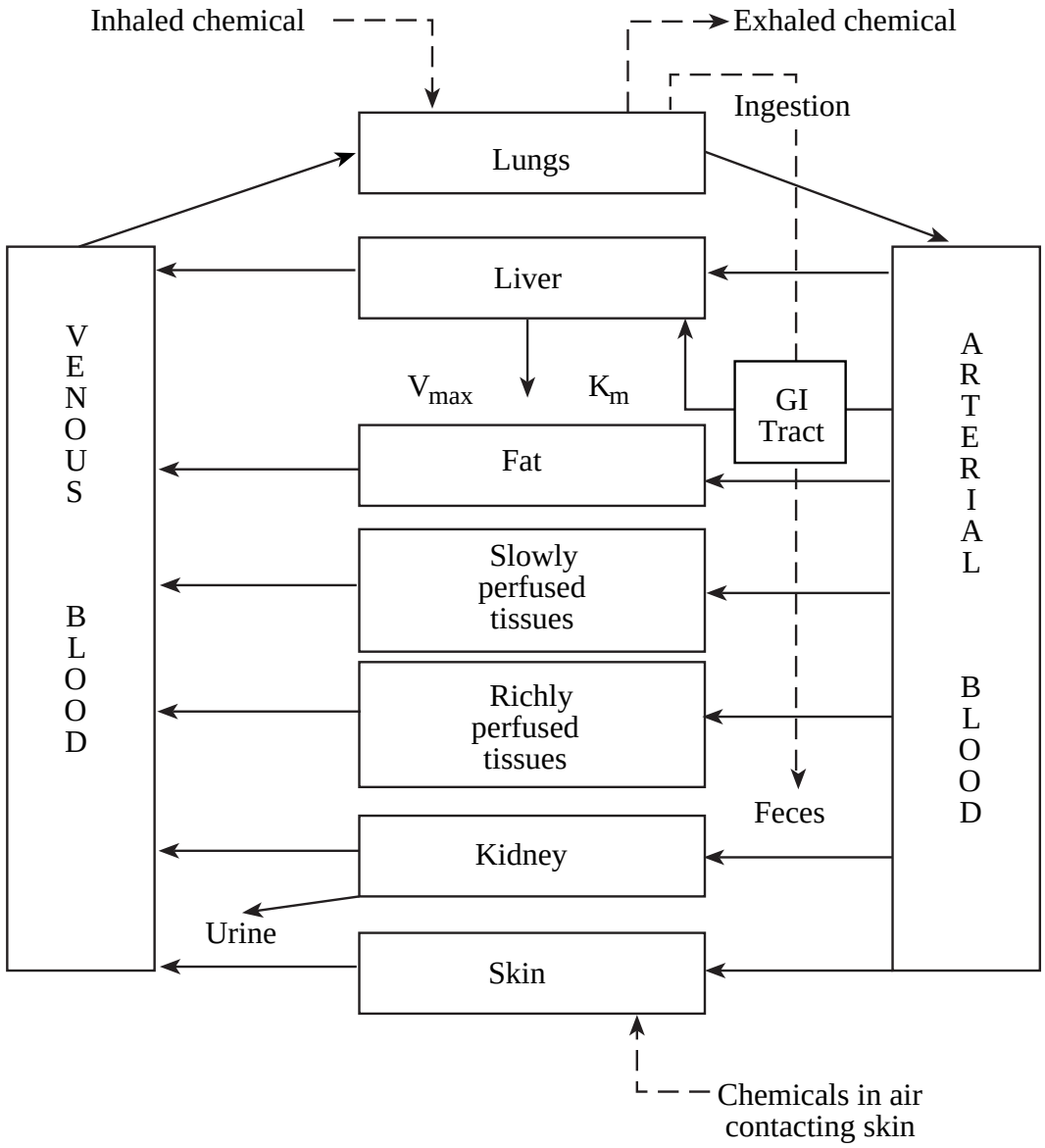
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

PBPK models are available that describe the kinetics of toluene after inhalation exposure; two for humans (Fisher et al. 1997; Pierce et al. 1996, 1999) and two for rats (DeJongh and Blaauboer 1996, 1997; Tardif et al. 1993). These models are all modifications of the standard four-compartment PBPK model developed for styrene (Ramsey and Andersen 1984) in which:

(1) absorption into the lung blood is assumed to be dependent on the inhaled concentration of toxicant, the concentration of toxicant in alveolar air, blood flow to the lung, the blood/air partition coefficient, and alveolar ventilation rates,
(2) exchange of toxicant between arterial blood and tissue compartments is flow-limited,

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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.

(3) changes in the amount of toxicant in three nonmetabolizing tissue compartments (adipose tissue, slowly perfused tissues, and rapidly perfused tissues) are described by mass transfer differential equations with tissue volume, blood flow through the tissue (i.e., tissue perfusion rate), arterial blood toxicant concentration, and tissue/blood partition coefficients as explanatory variables, and
(4) changes in toxicant amount in the liver (the fourth compartment) are described by similar differential equations that additionally include a Michaelis-Menten term for overall rates of toxicant metabolism.

The five-compartment human model for toluene developed by Pierce et al. (1996) includes an additional equation describing mass balance across the lung that has a Michaelis-Menten metabolic term (Pierce et al. 1996). The model assumes that toluene metabolism in the liver and lung are adequately described by subject-specific maximal rate constants for liver and lung ("Vmax-h and Vmax-p" of $52.1 \times BW^{0.7}$ µmol/hour and $0–0.7 \times 52.1 \times BW^{0.7}$ µmol/hour, respectively) and a common Km (5.97 µmol/L). The Km and Vmax-h values were based on those derived by fitting a Ramsey and Andersen-type four-compartment PBPK model (in which all parameters were constant except Vmax and Km) to toluene uptake data for rats placed in closed chambers at several initial toluene concentrations (Tardif et al. 1993). The human Vmax-h was estimated for each subject by multiplying the rat Vmax-h by the subject's body weight to the 0.7 power; the rat Km was taken as the human value (Pierce et al. 1996). The lung Vmax (Vmax-p) was estimated by model-fitting for each subject, allowing the value to range between 0 and 70% of the liver Vmax, Vmax-h. This procedure was based on observations that levels of CYP2E1 in human lung microsomes were 10.5% of liver activities (Wheeler et al. 1992), and 12 human liver samples showed a seven-fold range of CYP2E1 contents (Thummel et al. 1993).

Another singular feature of the Pierce human model is that subject-specific parameters such as age, height, weight, alveolar ventilation rate, adipose tissue fraction, and blood/air partition coefficient are put into the model (Pierce et al. 1996). Volumes of the tissue compartments in the model were scaled to each subject's body weight. Blood flows to the slowly and rapidly perfused tissues and the liver were taken as fractions of a standard human cardiac output scaled to body weight to the 0.74 power (in units of liter-hour), whereas subject-specific blood flows to the adipose tissue were estimated by model fitting (holding other parameters constant) allowing the fraction of cardiac output that perfuses adipose tissue to range between 0.06 and 0.18. The decision to "model-fit" this parameter within these bounds was based on published observations that adipose blood flows among individuals range widely from about 0.06 to

0.18 of total cardiac output. Tissue/blood partition coefficients used in the model for the slowly and rapidly perfused tissue, the liver, and adipose tissue were 1.54, 4.64, 4.64, and 55.9, respectively.

The initial development and validation of the human model involved comparing model fits with measured data (blood concentrations) for a group of 26 male volunteers who were exposed to 100 ppm toluene (50 ppm $^{1}H_{8}$-toluene and 50 ppm $^{2}H_{8}$-toluene) for a 2-hour period (Pierce et al. 1996). Venous blood concentrations of $^{1}H_{8}$- and $^{2}H_{8}$-toluene were measured at intervals for 120 hours post exposure. Prior to exposure, information on age, body weight, and adipose tissue fraction were obtained. During exposure, individual ventilation rates and blood/air partition coefficients for toluene were measured. Measures of the goodness-of-fit of the model predictions to the data were compared using subject-specific values, average values from the 26 subjects, and average literature values for: body weight, adipose tissue fraction, ventilation rate, blood/air partition coefficient, maximum velocity of pulmonary metabolism, and fraction of cardiac output to adipose tissue. The measured concentrations of toluene in blood showed a ten-fold interindividual range of variation. Subject-specific modeling explained 91% of the data variability, compared with 53% using literature values for model parameters (Pierce et al. 1996).

Pierce et al. (1998) used the human model to estimate toluene concentrations in alveolar breath reflective of exposure to 50 ppm toluene for 8 hours/day (the current ACGIH 8-hour TWA threshold limit value (TLV) for toluene). Calculated values were #10 μmol/m^3 for samples taken just before the final shift of a workweek and #150 μmol/m^3 postexposure. It was proposed that toluene breath sampling would be a rapid, noninvasive biomarker of toluene exposure in workers that is not contaminated by endogenous sources. Pierce et al. (1999) also used the human model as a research tool to ascribe differences in toxicokinetic behavior of $^{1}H_{8}$- and $^{2}H_{8}$-toluene to underlying physiological mechanisms.

Another human PBPK model has been developed for volatile organic compounds that models transfer of toxicant via lactation from a mother to a nursing infant, but *in vivo* pharmacokinetic data for toluene in breast milk were not available to validate this model (Fisher et al. 1997). This model is an adaptation of the Ramsey and Andersen design with the addition of a fifth compartment, a nonmetabolizing milk compartment with a varying volume. The model includes equations describing the rate of change in the amount of toxicant ingested by a nursing infant from the milk compartment, the rate of change in the amount of milk in the mammary tissue lumen, and the rate of change in the amount of toxicant in breast milk. The model used Michaelis-Menten kinetic constants for toluene metabolism in the liver estimated for rats (Vmax 7.5 mg/kg/hour; Km 0.3 mg/L); the rat Vmax was scaled for use in the model by multiplying it by a reference body weight (60 kg) to the 0.74 power. Human milk/blood partition

coefficients for 19 volatile organic chemicals were experimentally determined using samples from volunteers; the coefficient for toluene was 2.68. Other tissue/blood partition coefficients for toluene used in the model included 4.91 for rapidly perfused tissue and for liver, 1.61 for slowly perfused tissue, and 60.01 for adipose tissue.

Fisher et al. (1997) used the model to estimate the amount of toluene an infant would ingest via milk if the mother was occupationally exposed to toluene at the ACGIH (1999) Threshold Limit Value (TLV=50 ppm) throughout a workday. The model predicted that such an infant would have a daily intake of 0.46 mg toluene/day, which is below the U.S. EPA Health Advisory, 2.0 mg/day, for chronic ingestion of 1 L/day of toluene-contaminated water by a 10-kg child.

The four-compartment rat PBPK model for toluene developed by Tardif et al. (1993) restricted metabolism to the liver compartment. As described before, the Km (0.55 mg/L) and Vmax (4.8 mg/hour/kg) values were derived by fitting the model (in which all parameters were held constant except Vmax and Km) to toluene uptake data for rats housed in closed chambers for 5 hours at several initial toluene concentrations (75, 150, or 225 ppm) (Tardif et al. 1993). The model used 18.0 as the blood/air toluene partitioning coefficient, and the following for partitioning between blood and tissue groups: 4.64 for liver and rapidly perfused tissue, 1.54 for slowly perfused tissue, and 56.7 for adipose tissue. Reference rates for alveolar ventilation (15 L/hour/kg) and cardiac output (15 L/hour/kg) were scaled by a factor of body weight to the 0.74 power. Model predictions of venous blood concentrations in rats during and after 5-hour exposures to toluene concentrations of 75, 150, or 225 ppm compared favorably (by visual inspection) with empirical data.

Tardif et al. (1993) linked the rat PBPK model for toluene to a similar PBPK model for xylene via the metabolism term in the liver compartment to test if there was no metabolic interaction between these compounds or if a metabolic interaction existed that could be described by competitive, noncompetitive, or uncompetitive inhibitory interaction. A model with a competitive inhibition metabolic term provided the best visual fit to empirical data for air concentrations of toluene and xylene during 5-hour exposures of rats in a closed chamber to mixtures of toluene and xylene at several initial concentrations.

A five-compartment rat PBPK model developed by DeJongh and Blaauboer (1996) is similar in design to the Tardif rat PBPK model except that it contains an additional compartment, (i.e., the brain, which is assumed to be nonmetabolizing). The model used the same toluene partition coefficients used in the Tardif et al. (1993) rat model; the brain/blood partition coefficient, 2.0, was estimated from a published

value for the human brain/air coefficient and the rat blood/air coefficient. Reference rates for alveolar ventilation (14 L/hour/kg) and cardiac output (14 L/hour/kg) were scaled by a factor of body weight to the 0.74 power. With other parameters in the model held constant, models with different published values of Vmax and Km for toluene metabolism in rat liver from two *in vivo* and six *in vitro* rat studies were compared for their ability to fit empirical data from several studies for toluene blood concentrations or toluene brain concentrations in rats exposed to inhaled toluene. DeJongh and Blaauboer (1996) judged that a Vmax of 4.31 mg/kg/hour and Km of 0.26 mg/L gave the overall best fit to the empirical data, but noted that differences were generally small among predictions from models with the various values of Vmax and Km.

Dejongh et al. (1998) used their rat PBPK model for toluene and similar models for 14 other volatile organic chemicals to examine a hypothesis that the acute lethality of volatile organic chemicals is related to their ability to distribute into the brain. Using these models to calculate the dose in the brain associated with the LC_{50} for the compounds, it was noted that the products of the LC_{50} and their respective exposure durations ranged by about 60-fold, whereas the PBPK-derived brain doses associated with the LC_{50} ranged by about 6-fold. Dejongh et al. (1998) concluded that this observation supports the hypothesis that the acute lethality of volatile organic chemicals, including toluene, is directly related to the extent of their distribution into the brain.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. In humans and animals, toluene is rapidly absorbed by inhalation exposure (Benignus et al. 1984; Hjelm et al. 1988; Hobara et al. 1984b; Lof et al. 1993). Animal studies have shown that toluene is absorbed less rapidly by the oral route (Ameno et al. 1992; Pyykko 1983b), while toluene is absorbed slowly through human skin (Dutkiewicz and Tyras 1968). Studies with brush border membrane vesicles isolated from rat intestines and exposed to toluene indicate that toluene absorption occurs through the lipid matrix of the membrane (Alcorn et al. 1991).

Distribution. Toluene has been identified in brain, liver, lung, and blood in humans following toluene exposure (Paterson and Sarvesvaran 1983; Takeichi et al. 1986). Within the human brain, toluene has a greater affinity for areas of the brain that contain lipid-rich white matter, such as the brain stem, rather than the areas with larger amounts of grey matter (Ameno et al. 1992). The human data are supported by

animal studies where distribution of toluene was found to be characterized by uptake in lipid tissues (brain and fat) immediately following inhalation exposure (Ghantous and Danielsson 1986).

Excretion. In both humans and rats, up to about 75–80% of inhaled toluene that is absorbed can be accounted for by urinary excretion of the principal metabolite, hippuric acid (Lof et al. 1993; Ogata 1984; Tardif et al. 1998). Excretion of minor metabolites including S-benzyl mercapturic acid, S-*p*-tolulyl mercapturic acid, and conjugates of *ortho*- and *para*-cresol account for less than 5% of absorbed toluene. Excretion of nonmetabolized toluene in exhaled air can represent from 7 to 20% of absorbed toluene (Carlsson 1982; Leung and Paustenbach 1988; Lof et al. 1993). Although the liver is expected to be the main site of metabolism of toluene, CYP2E1, one of the principal isozymes catalyzing the initial reaction in the principal toluene metabolic pathway, has been detected in human lung microsomes at concentrations about 10-fold less than in liver microsomes (Wheeler et al. 1992). Under conditions in which the main pathway of toluene metabolism is inhibited by co-exposure with ethanol, exhalation of nonmetabolized toluene can become a principal route of excretion (Baelum et al. 1993).

2.4.2 Mechanisms of Toxicity

The mechanism by which acute exposure to toluene brings about neurological effects such as central nervous system depression and narcosis is generally thought to involve, at least in part, reversible interactions between toluene (the parent compound and not its metabolites) and components (lipids or proteins) of nervous system membranes. Support of parent-material involvement comes from the observation that pretreatment of rats with phenobarbital increased the rate of *in vivo* toluene metabolism and shortened the time of recovery from narcosis from single intraperitoneal doses of toluene (Ikeda and Ohtsuji 1971). Other support for this hypothesis includes the transient nature of anesthesia from acute high level exposure to toluene and the rapidity with which toluene-induced changes in brain biochemical variables can be measured. For example, within 0.25–1 hour of intraperitoneal injection of 1-g/kg doses of toluene into rats, brain synaptosomes showed decreased phosphatidylethanolamine content, altered phospholipid methylation activities, altered outer membrane fluidity, and increased Na+-K+-ATPase activities (Lebel and Schatz 1988, 1989, 1990). Decreased Mg++-ATPase activities were measured in brain synaptosomes isolated from rat brains immediately following a 2-hour exposure to 2,000 ppm toluene (Korpela and Tahti 1988). Average whole brain concentrations of several biogenic amines (dopamine, norepinephrine, and 5-hydoxytrytamine) were increased in rats immediately following an 8-hour exposure to 1,000 ppm toluene (Rea et al. 1984). On a molecular scale, the acute anaesthetic actions of toluene and other agents have been postulated to involve intercalation of toluene into the lipid

bilayer of nerve membranes and/or reversible interactions with proteins in the membrane (Franks and Lieb 1985, 1987).

Clinically obvious neurological impairment (e.g., gait and speech abnormalities) and brain atrophy have been observed in several cases of chronic toluene-inhalation abuse. MRI of the brain of solvent abusers (Filley et al. 1990; Rosenberg et al. 1988a, 1988b) suggest preferential atrophy in lipid-rich regions of the brain. Rosenberg et al. (1988a,1988b) found MRI evidence of diffuse central nervous system demyelination in 6 toluene abusers with clinically obvious neurological impairment, whereas Filley et al. (1990) noted that the degree of MRI-detected white matter abnormality in 14 solvent abusers was correlated with neurological impairment. The observed changes in MRI signals may be related to lipid compositional changes in the white matter, since these regions are more lipid-rich than gray matter (Ameno et al. 1992). These observations are consistent with a hypothesis that chronic exposure to high concentrations of toluene brings about structural changes in the brain related to lipid compositional changes. Supporting evidence for this hypothesis includes observations of changed phospholipid composition of rat brain synaptosomes following acute exposure to toluene (Lebel and Schatz 1988, 1989, 1990), decreased phospholipid concentrations in the cerebral cortex of rats following 30 days of continuous exposure to 320 ppm (Kyrklund et al. 1987), and decreased number of neurons in the hippocampus of rats, 4 months after exposure to 1,500 ppm toluene, 6 hours/day, 5 days/week for 6 months (Korbo et al. 1996). It is uncertain if toluene-induced changes in membrane phospholipid content may be caused by increased breakdown of phospholipids or inhibition of synthesis.

Mechanistic understanding is poor of effects that have been associated with intermediate and chronic exposure to toluene in workplace air such as increased symptoms of mild neurological impairment (Boey et al. 1997; Orbaek and Nise 1989; Ukai et al. 1993; Yin et al. 1987), performance deficits on neurobehavioral tests (Foo et al. 1990; Iregren 1982), hearing loss and changes in brainstem auditory-evoked potentials (Abbate et al. 1993; Morata et al. 1997; Vrca et al. 1996), and color vision impairment and changes in brainstem visual-evoked potentials (Muttray et al. 1997, 1999; Vrca et al. 1995, 1997a, 1997b; Zavalic et al. 1998a, 1998b, 1998c), but several mechanistic actions have been postulated.

One mechanistic hypothesis postulates that repeated interaction of toluene with membrane proteins and/or phospholipids in brain cells can change activities of enzymes involved in the synthesis and/or degradation of neurotransmitters and that levels of neurotransmitters at particular sites in the brain may be involved in producing subtle neurological effects. Some evidence for this hypothesis comes from observations of increased concentrations of dopamine, norepinephrine, and 5-hydroxytryptamine in rats exposed to

1,000 ppm for 8 hours (Rea et al. 1984) and in rats exposed to up to 105 mg/kg/day in drinking water for 28 days (Hsieh et al. 1990b), decreased dopamine levels and rates of turnover in several areas of the nucleus caudate in the brain of rats exposed to 80 ppm toluene, 6 hours/day for 3 days (Fuxe et al. 1982), increased levels of dopamine and noradrenaline in several brain regions in rats exposed to 80–3,000 ppm, 6 hours/day for 3 days (Andersson et al. 1983), and decreased activities of aromatic acid decarboxylase, an enzyme involved in synthesis of neurotransmitters, in the brain stem of rats exposed to 250 or 1,000 ppm, 8 hours/day, 5 days/week for 4 weeks (Bjornaes and Naalsund 1988).

Another mechanistic hypothesis postulates that repeated exposure to toluene may cause neurological effects by changing the binding of neurotransmitters to membrane receptors. In support of this hypothesis, persistent changes in brain-tissue dopamine D2 receptor binding and increased serum prolactin levels were found in rats 17 days after exposure to 80 ppm toluene 6 hours/day, 5 days/week for 4 weeks (von Euler et al. 1993, 1994). It was speculated that the increase in serum prolactin level could be related to a possible interaction between toluene and the pituitary dopamine D2 receptor; this receptor normally inhibits the release of prolactin into serum. Correlated with these biochemical changes were a significantly increased locomotor activity (approximately 2-fold) in response to injections of apomorphine (a dopamine) and a significantly increased escape latency (indicating impaired spatial learning and memory) in a water maze task, both observed 14–17 days after the 4-week toluene exposure (von Euler et al. 1994). Whether or not this hypothesis is related to effects observed in occupationally exposed humans is uncertain; Svensson et al. (1992b) did not find changes in serum prolactin levels in toluene-exposed printing workers compared with controls.

Significant decreases (28 or 47%) in rat brain glial fibrillary acidic protein (GFAP) induced by exposure to 1,000 ppm toluene, 6 hours/day for 3 or 7 days have been associated with increased serum levels of corticosterone (Little et al. 1998). The decreases in GFAP were observed in the thalamus and hippocampus, regions of the brain that are reported to be involved in controlling serum glucocorticoid levels and have high concentrations of glucocorticoid receptors, respectively (Little et al. 1998). Little et al. (1998) postulated that decreases in brain GFAP may be a consequence of toluene disruption of the hypothalamic-pituitary-adrenal axis and/or hormonal homeostasis, but noted that the available evidence is inadequate to firmly establish cause and effect. The possible mechanistic connections of these observations to toluene-induced changes in neurobehavior are uncertain.

There is evidence that hearing loss in animals induced by inhalation exposure to toluene is produced by toluene itself and not by its metabolites. Phenobarbital pretreatment, which increases the rate of *in vivo*

metabolism of toluene, prevented hearing loss in rats exposed to 1,500–2,000 ppm toluene, 8 hours/day for 7 days (Pryor et al. 1991). Rats that were given large gavage doses of ethanol (4 g/kg/day) and daily inhalation exposure to toluene concentrations of 1,750 ppm, 6 hours/day, 5 days/week for 4 weeks showed significantly greater hearing loss (as measured by auditory-evoked brainstem potentials) and outer hair cell loss in the ear than those exposed to toluene alone (Campo et al. 1998). Co-exposure to ethanol caused a significant decrease in hippuric acid urinary excretion rates compared with exposure to toluene alone, indicating that these large doses of ethanol inhibited the metabolism of toluene (Campo et al. 1998). Since exposure to ethanol alone in this study did not affect hearing or outer hair cell loss in the ear, ethanol inhibition of toluene metabolism and subsequent potentiation of toluene-induced loss of hearing are consistent with the idea that toluene itself is responsible for these effects. Mechanistic understanding at the molecular and cellular level is poor regarding how toluene exposure leads to a loss of outer hair cells in the ear and the degree to which toluene effects on neural cell membranes may be involved.

The molecular mechanism and pathogenesis of color vision impairment (dyschromatopsia) associated with occupational and intentional abusive exposure to toluene and other organic solvents are not clearly understood, but it has been postulated that toluene interference with dopaminergic mechanisms of retinal cells or toxic demylelinizaton of optic nerve fibers may be involved (Muttray et al. 1997, 1999; Zavalic et al. 1998a, 1998b, 1998c).

The postulated arene oxide intermediates formed in the metabolic pathway from toluene to *ortho*- or *para*-cresol are highly reactive and expected to bind to cell proteins and RNA, thereby potentially leading to cellular dysfunction and degeneration. Studies with human and rat liver microsomes and tissue slices showed that incubation with labeled toluene leads to incorporation of the label into microsomal proteins and RNA in an NADP-requiring reaction (Chapman et al. 1990). It does not appear likely, however, that this mechanism of action is the primary mode of toluene's toxicity, especially at air concentrations below 100 ppm that are of occupational and public health concern, because:

(1) the liver is expected to be the main site of toluene metabolism,
(2) the pathway to the cresol isomers accounts for less than 1–5% of metabolized toluene (see Section 2.3.3),
(3) results from animals studies and studies of toluene-exposed workers do not identify the liver as the most sensitive target organ (see Section 2.2.1.), and

(4) degenerative lesions in nervous tissues have not been detected by light microscopy in rats and mice exposed to concentrations as high as 1,200 ppm 6.5 hours/day, 5 days/week for up to 2 years (CIIT 1980; NTP 1990).

The available evidence, however, is not sufficient to discard the hypothesis that this mode of action (i.e., cellular degeneration caused by reactive metabolic intermediates) may play some role in toluene toxicity, especially with high-level exposures such as those experienced by toluene abusers.

2.4.3 Animal-to-Human Extrapolations

Many laboratory animal species have been used to describe toluene toxicity, but the most commonly used species is the rat. Generally, the toxicokinetic data gathered from rat studies compare favorably with the information available from human studies. In addition, neurological effects observed in rats including changes in locomotor activity, changes in visual- and auditory-evoked brainstem potentials, hearing loss, and changes in brain chemistry appear to be related to critical neurological effects observed in humans after acute or repeated exposure to toluene including self-reported neurological symptoms, impaired performance in neurobehavioral tests, hearing loss, and color vision impairment. Given the availability of data for humans exposed by inhalation, MRLs for inhaled toluene are derived without extrapolating from the available animal toxic-effects data. In contrast, acute and intermediate MRLs for oral exposure to toluene are based on extrapolating neurological effects in rats to humans (see Section 2.5 and Appendix A).

As discussed in Section 2.3.5, PBPK models describing the kinetics of toluene after inhalation exposure have been developed for humans (one with four compartments— adipose tissue, liver, and rapidly and slowly perfused tissues, and another with a fifth compartment—breast milk) and rats (one with the basic four compartments and another model with a fifth compartment—the brain). Further development of a human PBPK model that includes partitioning of inhaled and ingested toluene to the brain and a similarly designed rat PBPK model may be useful in improving extrapolation from the oral exposure rat data and in comparing model-based predictions of human effect levels based on neurological effects in inhalationally exposed rats with observed effect levels in humans exposed to airborne toluene.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Adverse effects on the nervous system are the critical effects of concern from acute, intermediate, or chronic exposure to toluene. Acute exposure is associated with reversible neurological symptoms progressing from fatigue, headaches, and decreased manual dexterity to narcosis with increasing exposure levels. Reversible neurological impairment from acute exposure likely involves the direct interaction of toluene with nervous system membranes. Degenerative changes in white matter regions of the brain have been correlated with the severity of persistent neurological impairment in individuals who abused solvents and have repeatedly inhaled toluene at high exposure levels (4,000–12,000 ppm). Results from studies of groups of occupationally exposed workers suggest that chronic exposure to toluene at lower exposure levels (from about 50 to 200 ppm) can produce subtle changes in neurological functions including cognitive and neuromuscular performance, hearing, and color discrimination. Supporting data come from studies of toluene-exposed animals showing changes in behavior, hearing loss, and subtle changes in brain structure, electrophysiology, and levels of neurotransmitters. Case reports of birth defects in children of mothers who abused toluene during pregnancy suggest that exposure to high levels of toluene may be toxic to the developing fetus. However, results from animal studies indicate that toluene is not a teratogenic agent, but can retard fetal growth and skeletal development and adversely influence behavior of offspring at exposure levels that overwhelm maternal mechanisms protecting the developing fetus from exposure. Other adverse health effects, including cancer or effects on reproductive performance, do not appear to be of concern for persons who may experience low exposures to toluene by living or working near hazardous waste sites containing toluene.

Issues relevant to children are explicitly discussed in Section 2.7, Children's Susceptibility and Section 5.6, Exposures of Children.

Minimal Risk Levels for Toluene.

Inhalation MRLs.

- An MRL of 1 ppm (3.8 mg/m^3) has been derived for acute-duration (14 days or less) inhalation exposure to toluene.

This MRL is based on a study by Andersen et al. (1983) in which the effects of toluene on 16 healthy young subjects with no previous regular exposure to organic solvents were investigated (see Appendix A). Groups of 4 subjects were in a chamber for 6 hours a day on 4 consecutive days. The concentration of toluene was 0, 10, 40, or 100 ppm, with the subjects exposed to a different concentration each day. Physiological measurements were performed, including nasal mucociliary flow, and subjective measurements of discomfort. Eight different performance assessment tests were carried out. There was a statistically significant increase (P<0.05%) in the occurrence of headaches, dizziness, and feelings of intoxication during the 100 ppm exposure, but not during exposure to the other concentrations. No statistically significant effects of toluene occurred in the eight performance tests. For 3 of the tests, there was borderline significance (P<0.10%): the subjects felt that the tests were more difficult and strenuous during the 100 ppm exposure. No adverse effects were reported at the 10 and 40 ppm levels. The NOAEL of 40 ppm was adjusted to continuous exposure basis
(40 ppmx5 days/daysx8 hour/24 hour=9.5 ppm) and divided by an uncertainty factor of 10 (to account for human variability) to derive the MRL of 1 ppm.

- No MRL has been derived for intermediate-duration (15–364 days) inhalation exposure to toluene.

No data were considered suitable for use in deriving an intermediate-duration MRL for inhalation exposures. ATSDR believes that the chronic inhalation MRL would also be protective for intermediate-duration exposures.

- An MRL of 0.08 ppm (0.3 mg/m^3) was derived for chronic-duration (365 days or more) inhalation exposure to toluene.

The chronic inhalation MRL is based on a LOAEL of 35 ppm toluene for color vision impairment in a group of toluene-exposed shoemakers studied by Zavalic et al. (1998a) and an uncertainty factor of 100 (10 for the use of a LOAEL and 10 to account for human variability). The study examined color vision abilities in three groups of workers: (1) 46 shoemakers exposed for an average of 16 years to a median toluene concentration of 32 ppm; (2) 37 rotogravure printing workers exposed for an average of 18 years to a median toluene concentration of 132 ppm; and (3) 90 control workers without any known exposure to solvents or neurotoxic agents. Average scores in a color confusion index (based on results of color vision tests and adjusted for age and alcohol intake) were significantly increased in the toluene-exposed shoemakers and printers compared with scores for control workers. The chronic LOAEL of 32 ppm is supported by observations of other subtle neurological effects in other groups of toluene-

exposed workers including altered visual-evoked brainstem potentials in printing press workers exposed to 50 ppm for 30 years (Vrca et al. 1995, 1996, 1997a, 1997b), altered auditory-evoked brainstem potentials in printers exposed to 97 ppm for 12–14 years (Abbate et al. 1993), hearing loss in printers exposed to 0.04–245 ppm toluene (Morata et al. 1997), changes in electro cardiographic R-R intervals in printers exposed to 83 ppm for 1–36 years (Murata et al. 1993), performance deficits in neurobehavioral tests in electronics workers exposed to 88–90 ppm (Boey et al. 1997; Foo et al. 1990), and increased incidence of self-reported neurasthenic symptoms in printers exposed to an average concentration of about 140 ppm over a 29-year period (Orbaek and Nise 1989).

Most of the data on health effects in humans exposed to toluene come from occupational studies or medical reports of solvent abusers. In both situations, concurrent exposure to other chemicals can limit the usefulness of the data for development of guidelines or standards. In addition, there are other confounding variables, especially in the occupational setting, such as alcohol consumption patterns, employment history, diet, use of medications, noise, and fluctuations in atmospheric toluene levels during different portions of the day, all of which complicate evaluation of dose-response patterns. These limitations were considered in selecting the studies for derivation of the MRLs.

ACGIH has recommended a TLV of 50 ppm toluene based on reports of headache and irritation associated with 4–6 hours continuous inhalation of toluene (Andersen et al. 1983; Baelum et al. 1985; Echeverria et al. 1989; Wilson 1943). This value is designed to be protective for healthy adult workers exposed 8 hours/day, 5 days/week for up to 45 years. Adjusting the value for a continuous exposure lasting up to 70 years yields a value of 8 ppm (50 ppm x 5 days/7 days x 8 hours/24 hours x 45 years/70 years=8 ppm). This figure is somewhat higher than the current chronic-duration MRL, but does not include an uncertainty factor to protect susceptible populations. Use of an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL) would arrive at a value to 0.08 ppm, which is identical to the current MRL.

Oral MRLs.

- An MRL of 0.8 mg/kg has been derived for acute (14 days or less) oral exposure to toluene.

This MRL was based on a LOAEL of 250 mg/kg from a study of flash-evoked potential (FEP) wave forms in male Long-Evans rats administered doses of 0, 250, 500, or 1,000 mg/kg toluene by gavage (Dyer et al. 1988). Flash-evoked potential tests were administered 45 minutes later as a test of the ability

of the nervous system to process visual information. The amplitude of the N3 peak of the FEP was decreased by toluene exposure at all doses (P<0.0001). This decrease in peak amplitude was not dose-related. Dyer et al. (1988) also carried out a time-course study in which toluene was administered to male Long-Evans rats (16 per group) at doses of 0 and 500 mg/kg by gavage and flash-evoked potential tests were performed 4, 8, 16, and 30 hours later. In the time course study, 500 mg/kg also decreased the amplitude of the flash-evoked potential; at this dose, little change in magnitude of peak N3 depression had occurred 8 hours posttreatment; by 16 hours recovery was complete. An uncertainty factor of 300 was used for this determination (3 for use of a minimally adverse LOAEL, 10 for interspecies extrapolation, and 10 for intraspecies variability).

- An MRL of 0.02 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to toluene.

This MRL was derived from a LOAEL of 5 mg/kg/day based on regional increases in monoamine neurotransmitters in the brains of CD1 mice exposed to toluene through their drinking water for 28 days (Hsieh et al. 1990b). Based on water consumption and average toluene concentrations, the authors calculated toluene doses for the 4 treatment doses of 0, 5, 22, and 105 mg/kg/day over this period. Brain levels of norepinephrine, dopamine, serotonin (5-hydroxytryptamine), and their metabolites vanillylmandelic acid, 3,4-dihydroxy-phenylacetic acid, homovanillic acid, and 5-hydroxyindolacetic acid were measured in six areas of the brain in the mice. Significant increases (P<0.05) in neurotramsmitter levels were seen in all six regions of the brain of animals gavaged with toluene; in general, the increase was maximal at 22 mg/kg/day. Significantly increased norepinephrine levels were present in the hypothalamus, midbrain, and medulla oblongata. Serotonin levels were significantly increased in the hypothalamus, midbrain, and cerebral cortex. The maximum increase of serotonin (P<0.005), dopamine (P<0.05), and norepinephrine (P<0.05) in the hypothalamus occurred at 22 mg/kg/day. In the corpus striatum, the levels of dopamine and serotonin were significantly increased at the two highest doses. In the medulla oblongata, significant toluene increases of norepinephrine and homovanillic acid were seen only at 22 mg/kg/day. It should be noted that these are minimal effects, and it is unclear how they are related to neurobehavioral changes. An uncertainty factor of 300 was used for this determination (3 for the use of a minimally adverse LOAEL, 10 for interspecies extrapolation, and 10 for intraspecies variability).

No MRL was derived for chronic-duration oral exposures because there were no suitable data for toluene.

Death. Case studies that reported on deaths in humans due to exposure to toluene have generally not provided information on dose and thus, do not provide a basis for quantitative estimates. In one instance, intake of 625 mg/kg resulted in death within 30 minutes (Ameno et al. 1989).

It has been suggested that the mechanism for death due to solvent abuse might be apparent sensitization of the myocardium and consequent sudden and severe arrhythmia resulting from mild anesthesia, and intensified by hypercapnia (excess of carbon dioxide) (Bass 1970). Studies in dogs further suggest that some individuals may be more sensitive to arrhythmic responses to toluene than others (Ikeda et al. 1990). In a single report of human death following oral ingestion of toluene, the cause of death appeared to be profound disruption of central nervous system function (Ameno et al. 1989). Exposure to toluene at a hazardous waste site is not likely to be of lethal magnitude.

Systemic Effects.

Respiratory Effects. The primary effect of toluene on the respiratory tract following inhalation is irritation. Studies with volunteers (Andersen et al. 1983; Carpenter et al. 1944; Baelum et al. 1985) and exposed workers (Parmeggiani and Sassi 1954) have demonstrated that toluene is a mild-to-moderate respiratory irritant. Early animal studies by von Oettingen et al. (1942) reported respiratory irritation and pulmonary lesions in rats exposed to high concentrations of toluene. The findings of von Oettingen et al. (1942) are supported by more recent observations of nasal lesions (including metaplasia of olfactory epithelium and degeneration of respiratory epithelium) in rats exposed to concentrations ranging from 600 to 1,200 ppm, 6.5 hours/day, 5 days/week for 2 years (NTP 1990). Mice exposed by the same exposure protocol to a similar range of concentrations, however, did not display upper or lower respiratory tract lesions (NTP 1990). Acute, intermediate, or chronic inhalation exposure to toluene at a hazardous waste site might result in respiratory tract irritation, especially if release of toluene is into an enclosed space where higher concentrations may develop, but other adverse effects on the lungs or breathing passages are not expected.

Cardiovascular Effects. Inhalation exposure to toluene at concentrations above 1,000 ppm has been associated with alterations of the heart rhythm in both humans and animals (Anderson et al. 1982; Einav et al. 1997; Ikeda et al. 1990; Magos et al. 1990; Meulenbelt et al. 1990; Vidrio et al. 1986), but exposure of rats or mice to concentrations as high as 12,000 ppm (3 hours/day) for intermediate durations or 1,200 ppm (6.5 hours/day) for chronic durations produced no histological changes in heart tissue (Bruckner and Peterson 1981b; CIIT 1980; NTP 1990). There may be intraspecies differences in the

cardiac response to toluene that make some individuals more susceptible than others to potentially fatal arrhythmias; the degree of hypoxia may also be important (Ikeda et al. 1990).

The exposure scenarios associated with cardiac rhythm disturbances were of the short-term, high-level type experienced by substance abusers. Accordingly, cardiovascular responses are not expected to occur following toluene exposure at or near a hazardous waste site, unless some occurrence releases a high concentration of toluene into an enclosed space.

Gastrointestinal Effects. The only gastrointestinal effect reported after exposure to toluene was ulceration of the forestomach of rats exposed to 600 and 1,200 ppm by inhalation for 2 years (NTP 1990). Similar effects were not seen in mice exposed under the same conditions or to rats or mice orally exposed to 2,500 mg/kg/day for 13 weeks (NTP 1990). There is a slight possibility that long-term toluene exposure resulting from the contamination of hazardous waste sites would cause gastrointestinal irritation in the exposed population.

Hematological Effects. Before the mid-1950s, chronic occupational exposure to toluene was associated with hematological effects (Greenburg et al. 1942; Wilson 1943). However, these effects are now attributed to benzene, a common contaminant of toluene at that time (EPA 1985c). In several recent studies, no significant effects of toluene on hematological parameters in workers exposed to toluene or a to mixture of solvents has been observed (Banfer 1961; Capellini and Alessio 1971; Ukai et al. 1993; Yin et al. 1987). In contrast, Tahti et al. (1981) reported a slight positive correlation between exposure and decreased blood leukocyte counts in workers. However, the authors did not report whether the workers were also exposed to other organic solvents. Therefore, effects that were observed cannot be attributed solely to toluene. Decreased leukocyte and white blood cell counts were observed in dogs and rats repeatedly exposed to airborne toluene (Hobara et al. 1984a; Horiguchi and Inoue 1977; von Oettingen et al. 1942), but have not been observed consistently in other studies of rats and mice exposed by inhalation (NTP 1990; Ono et al. 1996; Poon et al. 1994) or by oral administration (Hsieh et al. 1989; NTP 1990; Wolf et al. 1956). In the study by von Oettingen et al. (1942), rats exposed to high concentrations (2,500 or 5,000 ppm) of toluene for 7 hours each day had decreased leukocyte counts following exposure; however, the leukocyte numbers generally returned to normal by the next day. The toxicological significance of a transitory decrease in numbers of leukocytes is not apparent. Since effects on hematological variables have not been observed consistently in studies of occupationally exposed humans or in animals exposed to toluene, they are not expected to occur from acute, intermediate, or exposures at or near hazardous waste sites.

Musculoskeletal Effects. There is one case report of a man who had been sniffing glue containing toluene for 18 years. He complained of severe muscle weakness and was diagnosed with rhabdomyolysis (an acute disease of the skeletal muscles evidenced by myoglobin in the blood and urine) (Hong et al. 1996). However, it is not expected that any such effects would result from toluene exposure at or near a hazardous waste site.

Hepatic Effects. Studies of chronic toluene abusers or occupationally exposed humans have provided little evidence for serious liver damage due to inhaled toluene. Some studies of workers occupationally exposed to average concentrations between about 30 and 350 ppm toluene have reported liver effects such as increased serum levels of enzymes leaked from the liver (Guzelian et al. 1988; Svensson et al. 1992b), but others have recorded no adverse effects (Lundberg and Hakansson 1985; Seijii et al. 1987; Ukai et al. 1993). Results from studies of animals exposed by inhalation for acute (Ungvary et al. 1982; Wang et al. 1996), intermediate (Bruckner and Peterson 1981b; Kjellstrand et al. 1985; Kyrklund et al. 1987; NTP 1990; Poon et al. 1994), or chronic (NTP 1990) durations indicate that daily 6- to 8-hour exposures to concentrations above 300 ppm, but not below, can lead to increased liver weights (Bruckner and Peterson 1981b; NTP 1990; Poon et al. 1994; Ungvary et al. 1982) and induction of hepatic cytochrome P450 levels (Ungvary et al. 1982; Wang et al. 1996). There are a few reports of toluene-induced effects that may be associated with liver damage [e.g., increased serum levels of liver enzymes in rats exposed to 2,000 ppm for 48 hours (Tahti et al. 1983) and in rats exposed to 300 ppm, 6 hours/day for 4 weeks (Poon et al. 1994) and increased endoplasmic reticulum in hepatocytes after exposure of rats, mice, and rabbits to 795 ppm 8 hours/day for 7 days (Ungvary et al. 1982)], but no significant histopathological liver changes or liver weight changes were observed in well-conducted chronic-duration studies in which rats and mice were exposed to concentrations as high as 1,200 ppm, 6.5 hours/day, 5 days/week for 2 years (CIIT 1980; NTP 1990). Results from intermediate-duration oral-exposure studies in rats and mice support the idea that toluene does not cause degenerative liver effects, but, at sufficiently high doses, produces liver weight increases that are likely associated with enzyme induction (Hsieh et al. 1989; NTP 1990; Wolf et al. 1956). It is possible that exposure of the general population to toluene at hazardous waste sites may increase the ability of the liver to metabolize xenobiotics, but other hepatic effects are not expected if exposure levels are at or below those normally experienced in workplaces using toluene.

Renal Effects. The kidney may be a target of toluene toxicity in humans exposed to very high levels of toluene. Renal acidosis has been observed in solvent abusers exposed to toluene, but, in most cases, renal dysfunction is transient and normal function returns when exposure ceases (Gerkin and LoVecchio 1998; Goodwin 1988; Kamijima et al. 1994; Kamijo et al. 1998; Kaneko et al. 1992; Patel and Benjamin

1986; Taverner et al. 1988). These cases, however, are frequently confounded by probable exposure to multiple solvents. Renal effects have not been observed in workers exposed to levels of toluene up to 100–200 ppm for long durations (Askergren et al. 1981a; Nielsen et al. 1985). Animal studies indicate that inhalation of toluene causes kidney damage in rats (e.g., renal tubular casts), but only after intermediate or chronic exposure to concentrations $600 ppm for at least 6 hours/day (CIIT 1980; NTP 1990; von Oettingen et al. 1942). Histological evidence of kidney damage was not found in rats and mice exposed to gavage doses as high as 5,000 mg/kg/day for 14 or 15 weeks (NTP 1990). In general, the available human and animal data suggest that kidney damage is not likely to occur with acute, intermediate, or chronic exposure at toluene levels likely to be experienced by people who may live close to, but not work at, hazardous waste sites containing toluene.

Endocrine Effects. As discussed in more detail in Section 2.6, Endocrine Disruption, current data for toluene-exposed humans or animals provide suggestive, but not conclusive, evidence that toluene may cause some effects that may involve endocrine disruption including reports of increased abortions among female electronics workers (Ng et al. 1992b), changed levels of luteinizing hormone, follicular stimulating hormone, and testosterone in male printers exposed to toluene (Svensson et al. 1992a, 1992b), and increased serum levels of prolactin in rats exposed to 80 ppm toluene 6 hours/day, 5 days/week for 4 weeks (Andersson et al. 1983; Hillefors-Berglund et al. 1995; von Euler et al. 1993, 1994).

Other results from animal studies regarding possible endocrine disruption from toluene include decreased sperm counts and epididymides weight in male rats that were exposed to 2,000 ppm, 6 hours/day for 90 days but showed no exposure-related changes in mating behavior or fertility indices when mated after 60 days of exposure (Ono et al. 1996) and abundant vacuoles and mitochondrial degeneration in antral follicles of the ovaries of female rats exposed to 3,000 ppm, 8 hours/day for 7 days (Tap et al. 1996). Histopathological lesions in male or female reproductive organs, however, were not found in rats and mice exposed to gavage doses up to 2,500 mg/kg/day for 13 weeks or exposed (6–6.5 hours/day, 5 days/week) to concentrations up to 2,500 ppm for 14–15 weeks or 1,200 ppm for 2 years (NTP 1990).

Assessment of reproductive performance was not consistently affected by toluene in several other animal studies. Increased fetal mortality occurred after exposure of pregnant rats to 2,000 ppm, but not 600 ppm, 6 hours/day on gestation days 7–17 or 14 days before through 7 days after mating (Ono et al. 1995, 1996), and increased abortions occurred in pregnant rabbits exposed to 267 ppm, but not 133 ppm, 24 hours/day on gestation days 7–20 (Ungvary and Tatrai 1985). However, the number of pregnant mice producing viable litters was not affected following oral administration of 2,350 mg/kg/day on gestation

days 7–14 (Smith 1983). In addition, reproductive performance variables and offspring survival were not significantly affected in two generations of rats exposed to 2,000 ppm, 6 hours/day for up to 95 days (API 1985) or in rats exposed *in utero* to 1,200 ppm, 6 hours/day on gestation days 9–21 (Thiel and Chahoud 1997).

Dermal Effects. Skin irritation can occur in humans and animals dermally exposed to toluene (EPA 1983a; Winchester and Madjar 1986; Wolf et al. 1956). This appears to be due to the degreasing action of toluene and its removal of protective skin oils. It is uncertain if toluene dissolved in water at or near hazardous waste sites would have an effect on the skin of individuals who come in contact with the contaminated water.

Ocular Effects. Humans have reported eye irritation following exposure to toluene vapors (Andersen et al. 1983; Baelum et al. 1985; Carpenter et al. 1944, 1976; Meulenbelt et al. 1990). This is probably the result of direct contact of toluene vapor with the outer surface of the eye and thus, is not a true systemic effect. Slight to moderately severe irritation of rabbit eyes has been reported following direct application of toluene to the conjunctiva (Carpenter and Smyth 1946; Hazleton Laboratories 1962; Wolf et al. 1956). Reports of color vision deficits in occupationally exposed workers have been postulated to involve toluene interference with dopaminergic mechanisms of retinal cells or toxic demylelinizaton of optic nerve fibers (Muttray et al. 1997, 1999; Zavalic et al. 1998a, 1998b, 1998c).

Body Weight Effects. Weight loss has been reported to occur in rats exposed to toluene for periods of 11–23 weeks (Mattsson et al. 1990; Pryor 1991).

Immunological and Lymphoreticular Effects. Only limited data are available on the immunological effects of toluene. The studies by Lange et al. (1973) and Moszczynski and Lisiewicz (1985) report decreased T lymphocyte counts and decreased serum IgG and IgA levels in occupationally exposed workers, but no signs of diminished immunological function or disturbances in immune skin reactions against such antigens as tuberculin or distreptase. However, because the specific solvent(s) responsible for the effects observed in these studies was not identified, the significance of the findings for humans exposed to toluene are unclear.

Mice exposed to toluene for 4 weeks exhibited an increased susceptibility to infections (Aranyi et al. 1985). Ingestion of doses of 22 mg/kg/day toluene caused adverse effects on lymphocyte proliferation and interleukin-2 immunity in mice exposed through their drinking water. At higher doses

(105 mg/kg/day), additional effects upon the immune system were observed (decreased thymus weight, lymphocyte culture responses, and antibody plaque-forming cell responses) (Hsieh et al. 1989, 1990b). There are no data to suggest that these same responses occur in humans.

Neurological Effects. The nervous system is the critical target of toluene toxicity following acute, intermediate, or chronic inhalation or oral exposure to toluene. Studies with volunteers under controlled acute (6–8 hours) exposure conditions indicate that subtle neurological impairment is detectable in most subjects at concentrations in the 75–150 ppm range (Andersen et al. 1983; Baelum et al. 1985; Echeverria et al. 1991; Guzelian et al. 1988; Iregren 1986; Rahill et al. 1996). Concentrations of 200–800 ppm can produce exhilaration and light-headedness, and, at higher acute exposure concentrations, intellectual, psychomotor, and neuromuscular abilities are obviously impaired followed by development of narcosis (EPA 1985c; von Oettingen et al. 1942).

Numerous case studies have associated chronic inhalation exposure to toluene at levels inducing narcosis and euphoria (4,000 to 12,000 ppm as estimated by Gospe et al. 1994) with residual or permanent neurological damage as evidenced by abnormal electroencephalograms, structural changes in the brain detected by MRI and SPECT, tremors, paranoid psychosis, recurrent hallucinations, and impaired speech, hearing, and vision (Byrne et al. 1991; Caldemeyer et al. 1996; Devathasan et al. 1984; Filley et al. 1990; Hunnewell and Miller 1998; Ikeda and Tsukagoshi 1990; Kamran and Bakshi 1998; King et al. 1981; Maas et al. 1991; Meulenbelt et al. 1990; Miyagi et al. 1999; Rosenberg et al. 1988a, 1988b; Ryu et al. 1998; Suzuki et al. 1983; Yamanouchi et al. 1995). Studies of workers repeatedly exposed to toluene in workplace air at concentrations ranging from about 30 to 150 ppm have found evidence for increased incidence of self-reported neurological symptoms (Orbaek and Nise 1989; Yin et al. 1987), performance deficits in neurobehavioral tests (Boey et al. 1997; Foo et al. 1990; Orbaek and Nise 1989), hearing loss (Abbate et al. 1993: Morata et al. 1997), changes in visual-evoked brainstem potentials (Vrca et al. 1995, 1997a, 1997b), and color vision impairment (Zavalic et al. 1998a, 1998b, 1998c).

Studies with laboratory animals provide supporting evidence that the nervous system is the critical target of toluene toxicity. Acute (1 to 2 hours) inhalation exposure studies of behavior in rats, mice, and monkeys found evidence for stimulatory effects (e.g., increased locomotor activity, significantly increased response times) at concentrations ranging from 500 to 2,000 ppm, and central nervous system depression (e.g., decreased accuracy in conditioned response tests, decreased locomotor activity, and ataxia) at concentrations greater than 2,000 ppm (Bowen and Balster 1998; Bruckner and Peterson 1981a, 1981b; Bushnell et al. 1985; Hinman 1987; Taylor and Evans 1985). Rats exposed for 4 hours to

concentrations as low as 125 ppm toluene showed performance deficits in several trained neuromuscular responses (Kishi et al. 1988; Mullin and Krivanek 1982; Wood et al. 1983). Acute- and intermediate-duration inhalation exposure studies reported changes in several brain biochemical variables (e.g., dopamine levels, dopamine D2 receptor binding, changes in glial fibrillary acidic protein) in rats at exposure levels as low as 50–80 ppm for 6–8 hours/day (API 1997; Hillefors-Bergllund et al. 1995; Ikeda et al. 1986; Little et al. 1998; von Euler et al. 1989b, 1993, 1994). Neurological effects observed in animals after acute- or intermediate-duration oral exposure include changed flash-evoked potentials in rats given single gavage doses of toluene as low as 250 mg/kg (Dyer et al. 1988), changes in levels of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin) in several brain regions of mice exposed to 5–105 mg/kg/day in drinking water for 28 days (Hsieh et al. 1990b), and clinical signs of central nervous system dysfunction including ataxia, prostration, and tremors in rats and mice exposed to gavage doses $2,500 mg/kg/day for 13 weeks (NTP 1990). Other toluene-induced neurological effects reported in studies of animals with intermediate to chronic inhalation exposure include hearing loss in rats exposed to concentrations as low as 700–1000 ppm, 6–14 hours/day for 2–9 weeks (Campo et al. 1997, 1998; Johnson et al. 1988; Pryor and Rebert 1992; Pryor et al. 1984a, 1984b, 1991;), abnormal flash-evoked brain potential responses in rats exposed to 8,000 ppm for 15–35 minutes, 4–9 times/days for 13 weeks (Mattson et al. 1990), decreased weight of the total brain and the cerebral cortex, associated with decreased phospholipid content, in rats continuously exposed to 320 ppm for 30 days (Kyrklund et al. 1987), and decreased number of neurons in the hippocampus of rats, 4 months after exposure to 1,500 ppm toluene, 6 hours/day, 5 days/week for 6 months (Korbo et al. 1996).

Reproductive Effects. There is some evidence that women occupationally exposed to toluene, or wives of men similarly exposed, have an increased risk of spontaneous abortions (Lindbohm et al. 1992; Ng et al. 1992b; Taskinen et al. 1989). However, interpretation of these results is limited due to small sample size evaluated, an inability to define accurate exposure levels, failure to account for all possible confounding variables, and the difficulty in validating self-reported data. The occurrence of testicular atrophy (Suzuki et al. 1983) in one case of chronic solvent abuse cannot be specifically attributed to toluene exposure. Occupational exposure to increasing concentrations of toluene (8–<111 ppm) has been associated with decreased plasma levels of the luteinizing hormone, follicle stimulating hormone and testosterone levels in males (Svensson et al. 1992a, 1992b).

Results from the moderate number of animal studies examining reproductive end points following toluene exposure were discussed in detail in the Endocrine Effects portion of this section. These studies found some evidence for minor toluene-induced changes in male and female reproductive organs [e.g.,

decreased sperm count in male rats (Ono et al. 1995, 1996) and ultra structural changes in antral follicles in ovary of female rats (Tap et al. 1996)], but no histological evidence of structural damage to the reproductive organs in rats and mice exposed orally for intermediate durations or by inhalation for intermediate or chronic durations (NTP 1990). No evidence for impaired reproductive performance was found in several assays (Ono et al. 1995, 1996; Smith 1983; Thiel and Chahoud 1997), including a 2-generation study of rats exposed to up to 2,000 ppm, 6 hours/day (API 1985), except that exposure during pregnancy produced increased fetal mortality in rats exposed to 2,000 ppm, but not 600 ppm, 6 hours/day, on gestation days 7–17 or for 14 days before through 7 days after mating (Ono et al. 1995, 1996), and increased abortions in pregnant rabbits exposed to 267 ppm, but not 133 ppm, 24 hours/day on gestation days 7–20 (Ungvary and Tatrai 1985).

In general, the available results from studies of humans and animals suggest that toluene is not a potent reproductive toxicant, but may cause some reproductive problems, especially with repeated inhalation exposure during pregnancy to concentrations above 200 ppm.

Developmental Effects. There are a number of published reports of birth defects, similar to those associated with fetal alcohol syndrome, that have been described in children born to women who intentionally inhaled large quantities of toluene or other organic solvents during pregnancy (Arnold et al. 1994; Erramouspe et al. 1996; Goodwin 1988; Hersch 1988; Hersch et al. 1985; Lindemann 1991; Pearson et al. 1994). Defects described include microcephaly, central nervous system dysfunction, growth deficiency, cranofacial and limb abnormalities, and reversible renal tubular acidosis. Studies of women exposed during pregnancy to much lower concentrations of toluene in the workplace are restricted to a retrospective study of 14 women in Finland occupationally exposed to mixed solvents that suggested that solvent exposure may increase risk for central nervous system anomalies and neural tube closure defects (Holmberg 1979).

The reports of birth defects in solvent abusers suggest that high-level exposure to toluene during pregnancy can be toxic to the developing fetus. The available human data, however, do not establish causality between low-level or occupational exposure to toluene and birth defects, because of the small sample size and the mixed solvent exposure experienced by the subjects in the Holmberg (1979) study, the lack of other studies of possible birth defects in children of occupationally exposed women, and the likelihood that the high exposure levels experienced by pregnant solvent abusers (4,000–12,000 ppm) overwhelm maternal protection of the developing fetus from absorbed toluene. Experiments with pregnant mice demonstrated that 10-minute exposures to 2,000 ppm resulted in low uptake of toluene into

fetal tissue and suggest that, at lower exposure levels, absorbed toluene is preferentially distributed to maternal adipose tissue before distribution to the developing fetus (Ghantous and Danielsson 1986).

Studies of animals exposed during pregnancy found evidence for toluene-induced fetal resorptions and abortions in rabbits (Ungvary and Tatrai 1985) and skeletal retardation and anomalies in rats (Hudak and Ungvary 1978) at 24-hour/day exposure levels associated with maternal toxicity and mortalities (399 and 266 ppm for rabbits and rats, respectively). Other developmentally toxic effects in animals associated with less than continuous inhalation exposure to toluene (3–8 hours/day) during pregnancy include retarded skeletal development in rat fetuses at 266 ppm, 8 hours/day (Hudak and Ungvary 1978), decreased body weight in rat fetuses at 2,000 ppm, 6 hours/day (Ono et al. 1995), decreased body weight and increased incidence of unossified sternebrae in rat fetuses at $1500 ppm, 6 hours/day (Huntingdon Research Centre 1992a, 1992b), decreased fetal body weight and delayed vaginal opening in rat offspring at 1,000 ppm, 6 hours/day and increased preweaning offspring mortality at 1,200 ppm (Thiel and Chahoud 1997), decreased body weight and retarded skeletal development in mouse fetuses at 266 ppm, 3–4 hours/day (Ungvary and Tatrai 1985), and increased mouse litters with fetuses with enlarged renal pelves at 200 ppm, 6 hours/day (Courtney et al. 1986). Several inhalation studies have identified no-effect levels for toluene effects on standard developmental end points (e.g., implantations, resorptions, fetal body weight, and fetal visceral and skeletal malformations and variations) including 750 ppm, 6 hours/day on gestation days 6–15 for rats (Huntingdon Research Centre 1992b), 600 ppm, 6 hours/day on gestation day 7–17 for rats (Ono et al. 1995), 600 ppm, 6 hours/day on gestation days 9–21 for rats (Thiel and Chahoud 1997), 133 ppm, 3–4 hours/day on gestation days 6–15 for mice (Ungvary and Tatrai 1985), 133 ppm, 24 hours/day on gestation days 7–20 for rabbits (Ungvary and Tatrai 1985), and 500 ppm, 6 hours/day on gestation days 6–18 for rabbits (Klimisch et al. 1992).

In animal studies of oral exposure during gestation, developmentally toxic effects were not observed in pregnant mice exposed to oral doses of 1,800 or 2,350 mg/kg/day (Seidenberg et al. 1986; Smith 1983), but exposure of pregnant rats to gavage doses of 650 mg/kg /day toluene in corn oil on gestation days 6–19 produced offspring with decreased body weights, delayed ossification, smaller brain volumes, and decreased forebrain myelination per cell compared with controls (Gospe and Zhou 1998; Gospe et al. 1996).

Results from studies of neurobehavioral end points in rats following *in utero* exposure to toluene suggest that maternal exposure to airborne toluene concentrations above 1,200 ppm, 6 hours/day during late embryonic and fetal development can impair behavioral development of rat offspring (Jones and Balster

1997; Ono et al. 1995; Thiel and Chahoud 1997) and that drinking water exposure during gestation and lactation at doses of 106 mg/kg/day changes postweaning open-field locomotor activity in rat offspring (Kostas and Hotchin 1981).

The available animal studies suggest that toluene is not a potent teratogenic agent with *in utero* exposure, but can retard fetal growth and skeletal development and adversely influence development of behavior of offspring at exposure levels above those that form the basis of the inhalation and oral MRLs for toluene.

Genotoxic Effects. Results of *in vivo* studies of exposed humans (see Table 2-4) and *in vitro* microbial assays and other *in vitro* systems generally indicate that toluene is nonmutagenic and nongenotoxic (see Table 2-5). Richer et al. (1993) reported no significant effects on sister chromatid exchanges, cell cycle delay, and cell mortality in lymphocytes following exposure of 5 men to 50 ppm toluene over 3 consecutive days. However, an increase in the incidence of chromatid breaks, micronuclei, and sister chromatid exchanges in lymphocytes of workers exposed to toluene along with other chemicals has been reported (Bauchinger et al. 1982; Nise et al. 1991; Pelclova et al. 1990; Schmid et al. 1985). These studies of workers are confounded by concurrent exposure to other organic chemicals, small cohort size, and a lack of historical exposure monitoring data.

Cancer. Human and animal studies generally do not support a concern for the carcinogenicity of toluene. The only available human epidemiological studies were negative but inconclusive due to limitations in design. The validated animal inhalation bioassays were negative (CIIT 1980; NTP 1990); however, one available oral study showed a nondose-related increase in a variety of tumors (Maltoni et al. 1997). Thus, the data do not support a firm conclusion regarding the carcinogenicity of toluene.

2.6 ENDOCRINE DISRUPTION

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, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light 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

Table 2-4. Genotoxicity of Toluene *In Vivo*

Species (tests system)	End point	Results	Reference
Non-Mammalian cells:			
Grasshopper	Mitotic arrest	+	Liang et al. 1983
Mammalian cells:			
Rats	Chromosomal aberrations in bone marrow cells	+	Dobrokhotov and Enikeev 1977
Mice	Dominant lethal mutations in sperm cells	–	API 1981
Mice	DNA damage in blood, bone marrow and liver	–	Plappert et al. 1994
Human[a]	Chromatid breaks, gaps, and exchanges	+	Bauchinger et al. 1982
Human[a]	Chromosome changes	–	Forni et al. 1971
Human[a]	Sister chromatid exchange	–	Haglund et al. 1980
Human[a]	Chromosome changes	–	Maki-Paakkenen et al. 1980
Human[b]	DNA damage		Pitarque et al. 1999
Human[a]	Micronuclei and chromosome breaks	+	Nise et al. 1991
Human[a]	Aberrant cells and chromosome breaks	+	Pelclova et al. 1990
Human[a]	Sister chromatid exchange, cell cycle delay, cell mortality	–	Richer et al. 1993
Human[a]	Chromosome aberrations	+	Schmid et al. 1985
Human[a]	Sister chromatid exchange	–	Schmid et al. 1985

[a]Detected in peripheral lymphocytes
[b]Detected in leukocytes

+ = positive result; – = negative result

Table 2-5. Genotoxicity of Toluene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Bos et al. 1981
S. typhimurium (TA98, TA100, UTH8413, 8414)	Gene mutation	–	–	Connor et al. 1985
S. typhimurium (TA1535, PSK1002)	Gene mutation	No data	–	Nakamura et al. 1987
S. typhimurium	Gene mutation	No data	–	Nestmann et al. 1980
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	NTP 1990
Escherichia coli (P3478)	Gene mutation	No data	–	Fluck et al. 1976
Mammalian cells:				
Human lymphocytes	Sister chromatid exchange and chromosomal aberrations	No data	–	Gerner-Smidt and Friedrich 1978
Human lymphocytes	Sister chromatid exchange and chromosomal aberrations	No data	–	NTP 1990

– = negative result

compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997g). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Current data provide suggestive, but not conclusive, evidence that toluene may cause some endocrine effects. Most case studies of chronic abusers of toluene and other solvents have not reported effects on endocrine organs, but there are reports of effects that may be associated with endocrine disruption in groups of toluene-exposed workers including changed plasma levels of luteinizing hormone, follicular stimulating hormone, and testosterone in male printers exposed to toluene (Svensson et al. 1992a, 1992b), delayed time to pregnancy among wives of men exposed to mixed organic solvents including toluene (Sallmen et al. 1998), increased incidence of spontaneous abortions in female toluene-exposed electronics workers (Ng et al. 1992b), and incidences of spontaneous abortion above population norms in other small groups of toluene-exposed female workers or wives of male workers (Lindbohm et al. 1992; Taskinen et al. 1989). However, small numbers and lack of adjustment for possible confounding factors in some of these studies precludes drawing definite conclusions.

In animal studies, female rats exposed to 30 or 300 ppm, 6 hours/day, 5 days/week for 4 weeks showed a mild reduction in follicle size of the thyroid in one study (Poon et al. 1994), but results from several other studies in rats and mice found no histological evidence of toluene-induced changes in endocrine organs including the thyroid, adrenal glands, or pancreas following intermediate or chronic, oral, or inhalation exposure (API 1985, NTP 1990, Von Oettingen et al. 1942).

Exposure to toluene may damage the reproductive organs in animals, but whether this affects reproductive performance is unclear. Decreased sperm counts and decreased weights of the epididymides have been reported in male rats exposed to 2,000 ppm, 6 hours/day for 90 days (Ono et al. 1996). Exposure of female rats to 3,000 ppm, 8 hours/day for 7 days produced abundant vacuoles, lytic areas, and mitochondrial degeneration in the antral follicles of the ovaries (Tap et al. 1996). Increased relative testicular weights were reported in male mice exposed to 1,250 and 2,500 mg/kg/day by gavage for 13 weeks. However, no effects on the prostate, testes, uterus, or ovaries were observed in rats and female

mice gavaged with 312–2,500 mg/kg/day (NTP 1990), and no treatment-related histopathological lesions were found in the testes or ovaries of rats and mice exposed (for 6–6.5 hours/day) to concentrations up to 2,500 ppm toluene for 6.5 hours/day for 14–15 weeks or up to 1,200 ppm for 6–6.5 hours/day for 2 years (CIIT 1980; NTP 1990).

Assessment of reproductive performance was not consistently affected by toluene in several other animal studies. Increased fetal mortality was reported for rats exposed to 2,000 ppm for 6 hours/day from days 7–17 of gestation or from 14 days before mating until day 7 of gestation (Ono et al. 1995, 1996). Increased abortion was seen in rabbits continuously exposed to 267 ppm on days 7–20 of gestation, but not in mice exposed to 267 ppm for 3–4 hours/day on gestational days 6–15 (Ungvary and Tatrai 1985). However, the number of pregnant mice producing viable litters was not affected following oral administration of 2,350 mg/kg/day on gestation days 7–14 (Smith 1983). In addition, reproductive performance variables and offspring survival were not significantly affected in two generations of rats exposed to 2,000 ppm 6 hours/day for up to 95 days (API 1985) or in rats that had been exposed *in utero* to 1,200 ppm 6 hours/day on gestation days 9–21 (Thiel and Chahoud 1997).

There is evidence that toluene exposure can perturb the hypothalamic-pituitary axis in rats leading to persistent increases in serum levels of prolactin, but a study of toluene-exposed workers found no evidence for changed prolactin levels compared with control subjects (Svensson et al. 1992a, 1992b). Acute-to-intermediate duration exposure to 80 ppm toluene (6 hours/day for 4 weeks) increased serum levels of prolactin in rats 17 days after cessation of exposure, but not 29–40 days after exposure (Andersson et al. 1983; Hillefors-Berglund et al. 1995; von Euler et al. 1993, 1994). Von Euler et al. (1993, 1994) speculated that the increase in serum prolactin level could be related to a possible interaction between toluene and the pituitary dopamine D2 receptor which inhibits the release of prolactin into serum.

2.7 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 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 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 while 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).

Data from controlled-exposure studies of volunteers, studies of occupationally exposed humans, case reports of toluene abuse, and studies of animals after inhalation or oral exposure indicate that the nervous system is the critical target of toluene toxicity (see Sections 2.2, 2.3.4, and 2.5 for more details). The effects of toluene have not been thoroughly studied in children, but the limited available data suggest that the nervous system is also the most likely target of toluene toxicity in children. There are numerous reports of adolescents who repeatedly inhaled high levels (4,000–12,000 ppm) of toluene and developed persistent central nervous system dysfunction (e.g., Byrne et al. 1991; Devasthasan et al. 1984; King et al. 1981). Neurological effects associated with toluene exposure in juvenile animals include changed levels of brain neurotransmitters in rats, 7 weeks after 10-day exposure as newborns to 80 ppm, 6 hours/day (von Euler et al. 1989b); high frequency hearing loss in rats after exposure to 1,200 ppm for 14 hours/day for 5 or 9 weeks starting at weaning (Pryor and Rebert 1992; Pryor et al. 1984a); and decreased latency of escape from an electric shock in young rats (50 days old) exposed to 30,000–40,000 ppm toluene for 15 minutes/day for 30 days (Castilla-Serna et al. 1991).

Available information regarding age-related differences in toluene metabolism suggests that developing fetuses and children at very early stages of development may be more susceptible to toluene toxicity than adults, and that children past early neonatal periods may have the same capability as adults to dispose of toluene at low exposure levels . The capacity for metabolic detoxification of toluene is expected to be low in the developing human fetus because several CYP isozymes are either absent or expressed at very low levels (Leeder and Kearns 1997). However, rat studies indicate that levels of CYP isozymes involved in toluene metabolism are rapidly increased following birth and suggest that capabilities to carry out Phase I toluene metabolism at low exposure levels during neonatal periods may exceed those at sexual maturity and pregnancy (Nakajima et al. 1992b). CYP2E1, one of the principal CYP isozymes involved in the major toluene metabolic pathway (Nakajima et al. 1997; Tassaneeyakul et al. 1996), is expressed several hours after birth in humans and continues to increase during the first year of life (Vieira et al. 1996). Phase II enzymes involved in toluene metabolism (e.g., N-acetyl transferases, UDP-glucuronyl transferases, and sulfotransferases) also show changes during human neonatal development with adult activities present by 1–3 years of age (Leeder and Kearns 1997). There are other physiological differences between adults and children (e.g., children have higher brain mass per unit of body weight, higher cerebral blood flow per unit of brain weight, and higher breathing rates per unit of body weight:

see Snodgrass [1992]), but their contributions to possible age-related differences in susceptibility to toluene toxicity are currently uncertain.

Results from animal studies indicating that younger animals may be more susceptible to toluene toxicity than adults are restricted to markedly lower LD_{50} values for 14-day-old rats compared with adult rat values (Kimura et al. 1971) and more severe high frequency hearing loss in young rats exposed to toluene compared with adult rats (Pryor et al. 1984a). The human brain grows rapidly for the first 2 years life and continues more slowly until full brain cell numbers, complete myelination of subcortical white matter, and complete elaboration of dendrites and axons are attained at adulthood (Snodgrass 1992). It is unknown if the relatively long period of development of the human brain may make juvenile humans more susceptible to toluene toxicity than juvenile non primate animals.

Case reports of birth defects in solvent abusers suggest that high-level exposure to toluene during pregnancy can be toxic to the developing fetus (Arnold et al. 1994; Erramouspe et al. 1996; Goodwin 1988; Hersch 1988; Hersch et al. 1985; Lindemann 1991; Pearson et al. 1994). It is likely that the high exposure levels experienced by pregnant solvent abusers (4,000 to 12,000 ppm) overwhelm maternal mechanisms that protect the developing fetus from absorbed toluene at lower exposure levels. Experiments with pregnant mice demonstrated that 10-minute exposures to 2,000 ppm resulted in low uptake of toluene into fetal tissue and suggest that, at lower exposure levels, absorbed toluene is preferentially distributed to maternal adipose tissue before distribution to the developing fetus (Ghantous and Danielsson 1986).

Studies of pregnant rats, mice, and rabbits found no effects on standard developmental end points such as number of resorptions, fetal body weights, and incidences of fetuses or litters with malformations, after exposure during gestation to inhaled concentrations as high as 500–750 ppm, 6 hours/day (Huntingdon Research Centre 1992b; Klimisch et al. 1992; Ono et al. 1995; Thiel and Chahoud 1997; Ungvary and Tatrai 1985) and 133 ppm, 24 hours/day (rabbits only) (Ungvary and Tatrai 1985) or to oral doses as high as 1,800 or 2,350 mg/kg/day (Seidenberg et al. 1986; Smith 1983). Observed effects on fetal development in the available animal studies, at higher exposure levels that were not fatal to the fetuses or the mothers, were generally restricted to fetal body weight decrease, retardation of skeletal development, or minor skeletal or visceral anomalies without increased incidences of malformations (Courtney et al. 1986; Hudak and Ungvary 1978; Huntingdon Research Centre 1992a, 1992b; Ono et al. 1995; Thiel and Chahoud 1997; Ungvary and Tatrai 1985). Neurological effects observed in animal offspring following gestational exposure to toluene include smaller brain volumes and decreased forebrain myelination per

cell in offspring of pregnant rats exposed to 650 mg/kg/day during gestation (Gospe and Zhou 1998; Gospe et al. 1996) and behavioral changes in offspring of pregnant rats exposed by to airborne concentrations above 1,200 ppm, 6 hours/day (Jones and Balster 1997; Ono et al. 1995; Thiel and Chahoud 1997) or to drinking water doses of 106 mg/kg/day (Kostas and Hotchin 1981).

In general, available information suggests that toluene is not a potent teratogenic agent with *in utero* exposure, but can retard fetal growth and skeletal development and adversely influence development of behavior of offspring at exposure levels above those that form the basis of the inhalation and oral MRLs for toluene.

Transfer of toluene to nursing infants from breast milk of currently exposed mothers is expected to be a possibility because of the lipophilicity of toluene and the relatively high lipid content of breast milk. Elimination kinetics data for nonpregnant or nonlactating humans and rats following toluene exposure, however, indicate that most absorbed toluene is rapidly eliminated from the body and that a much smaller portion (that which gets into adipose tissues) is slowly eliminated (Leung and Paustenbach 1988; Lof et al. 1993; Pierce et al. 1996, 1999; Pellizzari et al. 1992; Rees et al. 1985; see Section 2.3.4). Thus, mobilization during pregnancy or lactation of stored toluene from pre conception exposure does not appear to be a major concern.

Fisher et al. (1997) developed a human PBPK model that predicts transfer of toxicant via lactation from a mother to a nursing infant and used the model to estimate the amount of toluene an infant would ingest via milk if the mother was occupationally exposed to toluene at the ACGIH (1999) Threshold Limit Value (TLV=50 ppm) throughout a workday. The model predicted that such an infant would have a daily oral intake of 0.46 mg toluene/day. This value is below the U.S. EPA Health Advisory, 2.0 mg/day, for chronic ingestion of 1 L/day of toluene-contaminated water by a 10-kg child and a daily oral intake for a 10-kg child (8 mg/day) associated with the acute oral MRL for toluene (0.8 mg/kg/day). However, this value is above the daily oral intake for a 10-kg child (0.2 mg/day) associated with the intermediate oral MRL for toluene (0.02 mg/kg/day), suggesting there may be some concern for neurological effects in suckling infants exposed for more than 14 days to breast milk from mothers exposed during lactation to concentrations of 50 ppm in workplace air. It should be noted, however, that no human (or animal) studies were located regarding *in vivo* distribution of toluene into breast milk or elimination kinetics from breast milk, and the Fisher et al. (1997) PBPK model has not been validated with *in vivo* data.

2.8 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to toluene are discussed in Section 2.8.1.

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 toluene are discussed in Section 2.8.2.

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 2.10 "Populations That Are Unusually Susceptible".

2.8.1 Biomarkers Used to Identify or Quantify Exposure to Toluene

The biological exposure indices recommended by ACGIH (1999) to assess exposure of workers to toluene in the workplace are *ortho*-cresol and hippuric acid levels in urine at the end of a workshift and toluene levels in blood immediately prior to the last shift of a workweek. However, there are no markers of toluene exposure that persist in the body for an extended period of time after exposure has ceased.

The most accurate biomarker of toluene exposure is the presence of toluene in serum or blood, but measurements of toluene or its metabolites in urine are often preferred as urine sampling is less invasive. Measurements of toluene in serum, blood, and urine taken at the end of shift were significantly correlated with measurements of toluene concentrations from personal air monitors (Kawai et al. 1992a, 1992b, 1996). Measurement of toluene in blood was more sensitive than measurement of toluene in urine for detecting toluene at low concentrations (Kawai et al. 1992a). It is not necessary to draw large quantities of blood for analysis since toluene concentrations from capillary blood samples were also highly correlated (r=0.94) with toluene concentrations in exhaled air (Foo et al. 1991).

Although measurement of urinary excretion of toluene metabolites (hippuric acid, mercapturic acids, *ortho*-cresol and *para*-cresol) is a less invasive method than blood sampling for determining toluene exposure, the presence of these compounds in the urine is not definitive proof of toluene exposure since they are also produced by metabolism from the normal diet (Baelum 1990; Hjelm et al. 1988; Lof et al. 1993; Maestri et al. 1997). It has also been reported that the presence of toluene in urine is a more sensitive biomarker for toluene exposure than the presence of hippuric acid or ortho-cresol (Kawai et al. 1996). In addition, the background levels of these metabolites may be affected by individual variability (Lof et al. 1993), ethnic differences (Inoue et al. 1986), or other factors such as alcohol consumption and smoking (Kawamoto et al. 1996; Maestri et al. 1997). Despite these limitations, a number of authors have shown a correlation between the levels of these metabolites in urine and toluene exposure (Angerer and Kramer 1997; Angerer et al. 1998a; Kawai et al. 1992a, 1992b, 1996; Nise 1992; Truchon et al. 1996) and they have been widely used as biomarkers of toluene exposure.

2.8.2 Biomarkers Used to Characterize Effects Caused by Toluene

There are no specific biomarkers used to characterize the effects from toluene exposure. Changes in the brain, which are detected through magnetic resonance imaging (MRI) or brainstem auditory evoked response (BAER) techniques in combination with an exposure history, can be used to evaluate the degree of central nervous system damage experienced by a known toluene abuser. This approach does not appear to offer potential as a method of measuring the effects of short- or long-term minimal exposures as are likely to occur with environmental releases. A detailed discussion of the effects of toluene exposure is included in Section 2.2.

Additional information concerning biomarkers for effects on the immune, renal, and hepatic systems can be found in the CDC/ATSDR Subcommittee Report on Biological Indicators of Organ Damage (CDC/ATSDR 1990), and on the neurological system in the Office of Technology Assessment Report on Identifying and Controlling Poisons of the Nervous System (OTA 1990).

2.9 INTERACTIONS WITH OTHER CHEMICALS

Alteration of toluene metabolism may influence toluene's toxic effects because toluene metabolism predominately represents a detoxification process (see Section 2.4.2). Hypothetically, compounds that stimulate or inhibit metabolism of toluene may respectively decrease or increase toluene toxicity, although the possible exhalation of unmetabolized toluene represents an alternate dispositional pathway that may be utilized under conditions inhibiting mainstream toluene metabolism. Several metabolic interactions between toluene and other chemicals have been studied. The results present evidence that alteration of toluene metabolism may influence toluene toxicity and that toluene can influence the toxicity of other chemicals.

Phenobarbital pretreatment, which increases the rate of *in vivo* metabolism of toluene by inducing CYP isozymes, prevented hearing loss in rats exposed to 1,500–2,000 ppm toluene, 8 hours/day for 7 days (Pryor et al. 1991). Conversely, rats that were given large gavage doses of ethanol (4 g/kg/day) and daily inhalation exposure to toluene concentrations of 1,750 ppm, 6 hours/day, 5 days/week for 4 weeks showed significantly greater changes in auditory-evoked brainstem potentials and outer hair cell loss in the ear than those exposed to toluene alone (Campo et al. 1998). Co-exposure to ethanol caused a significant decrease in hippuric acid urinary excretion rates compared with exposure to toluene alone, indicating that these large doses of ethanol inhibited the metabolism of toluene (Campo et al. 1998).

Consistent with the idea that co-exposure to ethanol inhibits toluene metabolism are observations that ingestion of ethanol prolongs the presence of toluene in blood in humans (Imbriani and Ghittori 1997; Wallen et al. 1984) and rats (Romer et al. 1986). These results indicate that toluene-induced hearing loss is caused by toluene itself and not its metabolites, and that workers exposed to toluene who regularly drink alcohol may be at greater risk of developing toluene-related neurological problems than non drinkers.

Concurrent chronic ethanol ingestion and acute toluene inhalation in rats was associated with a modest elevation in plasma aspartate aminotransferase and increases in relative liver weight and liver triglycerides (Howell et al. 1986). Toluene also antagonized the hypertriglyceridemia associated with chronic ethanol ingestion. This study suggests that combined ethanol and chronic occupational toluene exposure may have the potential to augment alcohol-induced fatty liver.

Benzene, xylene, and toluene are metabolized through cytochrome P-450 oxidation. Benzene is converted to phenol, hydroquinone, catechol, and phenyl mercapturic acid; xylene is converted to methyl hippuric acids, and toluene forms hippuric acid, o-cresol, and p-cresol. The excretion of metabolites was investigated in four groups of workers who were exposed in the workplace to benzene and toluene, to a mixture of both solvents, or to no solvents (Inoue et al. 1988). Analysis of the data on excretion of urinary metabolites indicated that simultaneous exposure to both benzene and toluene inhibited the microsomal metabolism of both compounds through the cytochrome P-450 system. Toluene had more of an inhibitory effect on benzene metabolism than benzene had on toluene metabolism. This observation was confirmed in rodent studies using 6-hour inhalation exposures to benzene, toluene, or a mixture of both compounds, with pharmacokinetic modeling of the exposure data (Purcell et al. 1990). Combinations of either 200 ppm toluene with 1,000 ppm benzene or 1,000 ppm toluene with 200 ppm benzene were tested. The fit of the actual closed chamber concentrations for the individual chemicals with the model results, suggests that the interaction of benzene and toluene are noncompetitive. The data from studies of the benzene-toluene interaction may indicate that workers exposed to mixtures of both solvents have a lower risk of benzene-induced leukopenia than workers exposed to benzene alone (Purcell et al. 1990).

Toluene and xylene are also often found together in mixtures such as paint thinners. Human exposure to low levels of both solvents (50 ppm xylene, 40 ppm toluene) did not modify the conversion of either substance to its urinary metabolites (Kawai et al. 1992b; Tardif et al. 1991). However, at higher concentrations (80 or 150 ppm xylene, 95 or 150 ppm toluene), the blood and exhaled air concentrations

of both solvents were increased compared to the controls exposed to either solvent alone, indicating that metabolism of both solvents was decreased by the coexposure paradigm (Tardif et al. 1991, 1992). Similarly, coexposure of toluene, methyl ethyl ketone and isopropyl alcohol at low concentrations in rats had no effect on the urinary excretion of hippuric acid, while high concentrations resulted in decreased levels of hippuric acid (Uaki et al. 1995). Tardif et al. (1993) reported that a linked PBPK model for toluene and xylene with a competitive inhibition metabolic term provided the best visual fit (compared with non- or competitive inhibition metabolic terms) to empirical data for air concentrations of toluene and xylene during 5-hour exposures of rats in a closed chamber to mixtures of toluene and xylene at several initial concentrations.

Toluene and *n*-hexane, which are used together in some glues and paints, are neurotoxic chemicals that act by different modes at different sites. Toluene effects on the central nervous system are thought to be facilitated by toluene itself, whereas *n*-hexane affects the peripheral nervous system through the production of a toxic metabolite, 2,5-hexanedione (Ali and Tardif 1999). The initial metabolism of both compounds has been demonstrated to principally involve CYP isozymes including CYP2E1 and CYP2B6 (Ali and Tardif 1999). Under *in vitro* conditions with rat liver microsomes, a noncompetitive inhibition of each other's metabolism was demonstrated (Perbellini et al. 1982). In studies comparing urinary excretion of metabolites in rats exposed to mixtures of toluene and *n*-hexane or to each solvent alone, co-exposure inhibited the urinary excretion of 2,5-hexanedione to a larger extent than the urinary excretion of toluene metabolites, hippuric acid, and *ortho*-cresol (Ali and Tardif 1999; Iwata et al. 1983; Perbellini et al. 1982). The results from these studies suggest that toluene is a more effective inhibitor of *n*-hexane metabolism than is *n*-hexane of toluene metabolism. Co-exposure of rats to 1,000 ppm toluene and 1,000 ppm *n*-hexane (12 hours/day for 16 weeks) decreased toxic effects of *n*-hexane on the peripheral nervous system compared with exposure to 1,000 ppm *n*-hexane alone (Takeuchi et al. 1981). Another rat study found confirming results in that co-exposure to 1,200 ppm toluene and 4,000 ppm *n*-hexane (14 hours/day for 9 weeks) decreased *n*-hexane-induced effects on the peripheral nervous system compared with *n*-hexane alone, and had only slight effects on toluene-induced hearing loss and motor dysfunction compared with toluene alone (Pryor and Rebert 1992). Human and rat PBPK models have been developed to model the combined exposure and disposition of inhaled toluene and *n*-hexane (Ali and Tardif 1999; Yu et al. 1998). Model simulations predicted that co-exposure to *n*-hexane and toluene at constant concentrations corresponding to their occupational exposure limits (50 ppm) would lead to only a slight effect on the kinetics of their respective metabolism and disposition, but that the interaction could change with fluctuations in worker activity loads and workplace air concentrations (Ali and Tardif 1999; Yu et al. 1998).

An individual's drug therapy can have an influence on toluene toxicity. Haloperidol (an antipsychotic) functions by blocking dopamine receptors in the brain. The combination of haloperidol with toluene exacerbates dopamine depletion in several areas of the brain, thus changing the pharmacodynamics of the haloperidol. Individuals who take haloperidol should be counseled by their physician if environmental or occupational exposure to toluene is possible (von Euler et al. 1988b).

Studies in humans and rats indicate that the common analgesics, acetaminophen and aspirin, may inhibit toluene metabolism and influence toluene toxicity. CYP2E1 is involved in the initial step of the principal metabolic pathway for toluene and acetaminophen, and represents a potential site for a competitive metabolic interaction. Aspirin and one of the principal downstream metabolites of toluene, benzoyl coenzyme A, are conjugated with glycine. When glycine pools are depleted by competition for glycine by aspirin metabolism, toluene metabolism may be inhibited. In volunteers exposed for 4 hours to 300 mg/m^3 toluene (80 ppm) with or without doses (1,000 mg/70 kg=14.3 mg/kg) of acetaminophen (paracetamol) or acetyl salicylic acid (aspirin), co-exposures with these analgesics increased the concentration of toluene in the blood compared with exposure to toluene alone (Lof et al. 1990). Acetaminophen co-exposure also significantly increased the area under the blood concentration versus time curve and the apparent blood clearance of toluene, consistent with an inhibition of toluene metabolism. Co-exposure of rats for 10 days to higher oral doses of aspirin (acetyl salicylic acid: 100 mg/kg, twice daily) and inhalation exposure to toluene (1,000 ppm, 14 hours/day) caused a more severe loss of hearing (assessed 2–5 days or 4 months after cessation of exposure) compared with exposure to toluene alone (Johnson 1992). Treatment with aspirin alone at these doses did not cause hearing loss in the rats. These results are consistent with the hypothesis that high doses of aspirin may potentiate toluene effects on hearing by inhibiting toluene metabolism.

The benzoic acid metabolite of toluene is conjugated with glycine to produce hippuric acid. Toluene potentiation of developmentally toxic effects in rats from high doses of aspirin has been attributed to metabolic competition for glycine pools (Ungvary et al. 1983). Pregnant rats that were given 250 mg/kg acetyl salicylic acid on gestation day 12 and exposed to toluene at concentrations of 1,000, 2,000, or 3,600 mg/m^3 (265, 531, or 956 ppm) on gestation days 10–13 showed maternal effects (decreased food consumption and body weight gain and increased relative liver weight) and fetal effects (retardation of skeletal development and increased incidence of fetal malformations) that were more severe than those observed in rats exposed to 250 mg/kg acetyl salicylic acid alone. The effects were comparable in severity to those observed in rats exposed to 500 mg/kg salicylic acid alone. In this study, no maternal or fetal effects were observed in a group of rats exposed to 956 ppm toluene on gestation days

10–13 without coexposure to acetyl salicylic acid. The maternal and fetal effects of co-exposure to acetyl salicylic acid and toluene were diminished to the severity of the 250-mg/kg acetyl salicylic acid alone level when the administration of the acetyl salicylic acid dose was preceded by two hours with a gavage dose of 5,000 mg/kg glycine.

2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to toluene than will most persons exposed to the same level of toluene 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 toluene, or compromised function of organs affected by toluene. Populations who are at greater risk due to their unusually high exposure to toluene are discussed in Section 5.7, Populations With Potentially High Exposures.

The main target organ of toluene is the central nervous system, and it is generally thought to be due at least in part, to reversible interactions between toluene (the parent compound, not its metabolite) and the lipid or protein components of nervous system membranes (mechanisms of toxicity are discussed in detail in Section 2.4.2). The main pathway of toluene metabolism leads to the production of hippuric acid, which is excreted in the urine. The predominant first step in human and rat metabolism of toluene is catalyzed primarily by the CYP 2E1 isozyme. Later steps in this pathway involve the enzymes alcohol dehydrogenase, aldehyde dehydrogenase, acyl-coenzyme A synthase, and acyl-coenzyme A:amino acid N-acyl transferase (metabolism is discussed in detail in Section 2.2.3).

Environmental or genetic factors that decrease the capacity for metabolic detoxification of toluene are likely to increase susceptibility. This is supported by experiments in which inhibiting or enhancing toluene metabolism respectively enhanced of inhibited toluene-induced hearing loss in rats (Campo et al. 1998; Pryor et al. 1991). Chronic consumers of alcohol, and users of any medication that interfered with toluene metabolism, would be likely to have an increased risk for this reason. Differences in the relative efficiency of enzymes found in ethnic populations may also lead to differences in toluene susceptibility. For instance, ethnic variations in the occurrence of CYP isozymes, alcohol dehydrogenase, and aldehyde dehydrogenase are known to exist (Kawamoto et al. 1995, 1996; Kim et al. 1997).

Nutritional status may also affect susceptibility to toluene. Liver metabolism of toluene in rats fasted for 1 day was significantly increased compared with rats that had been fed (Nakajima and Sato 1979).

However, long-term malnutrition may increase susceptibility to the developmental effects of toluene. Skeletal development in the fetuses of rats that were malnourished throughout pregnancy and injected with 1.2 g/kg/day toluene was retarded to a significantly greater extent than in the fetuses of well-nourished dams injected with toluene (da Silva et al. 1990).

Individuals with pre-existing medical conditions may also be more susceptible to the effects of toluene. Individuals with pre-existing defects in heart rhythm may have a greater risk than healthy individuals for experiencing tachycardia or cardiac fibrillation following exposure to high levels of toluene. The presence of toluene in the air reduces the concentration of oxygen and can lead to hypoxia when exposure concentrations are high. Thus, individuals with asthma or other respiratory difficulties may be at increased risk with exposure to high atmospheric concentrations of toluene. Genetic predisposition for hearing loss may increase the risk for toluene-induced ototoxicity (Johnson 1992; Li et al. 1992).

2.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Aaron, CK and Howland, MA (eds.). 1994. *Goldfrank's Toxicologic Emergencies*. Appleton and Lange, Norwalk, CT.

Dreisbak, RH (ed.). 1987. *Handbook of Poisoning*. Appleton and Lange, Norwalk, CT.

Ellenhorn, MJ and Barceloux, DG, (eds.). 1988. *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. Elsevier Publishing, New York, NY.

Haddad, LM and Winchester, JF (eds.). 1990. *Clinical Management of Poisoning and Drug Overdose*. 2nd edition, WB Saunders, Philadelphia, PA.

2.11.1 Reducing Peak Absorption Following Exposure

The absorption of toluene is rapid and virtually complete following inhalation and oral exposures. Toluene appeared in the blood of 10 human subjects within 10–15 minutes of exposure to 78 ppm toluene

in the air, signifying rapid absorption through the lungs. When exposure occurs by the oral route, uptake into the blood is expected to be slightly slower due to the time needed for transit to the small intestines. Since toluene is absorbed across the lipid matrix of the cell membrane (Alcorn et al. 1991) some absorption can occur from the mouth and stomach. However, most of the toluene will be absorbed through the intestines due to large exposed surface area of the villi and microvilli. Other factors that will influence uptake from the gastrointestinal tract are lipid content of the gastrointestinal contents and the magnitude of the toluene exposure. Absorption of inhaled toluene is increased by exercise and so a reduction of physical activity during exposure is likely to reduce absorption (Rahill et al. 1996). However, there is really no effective way to reduce peak absorption following inhalation exposure. Emesis is contraindicated in cases of toluene ingestion due to the risk of aspiration. The use of activated charcoal and lavage may help to reduce oral exposure and rapid rinsing of the skin with water or washing with soap and water will reduce the opportunity for dermal absorption. If the eyes are affected, proper rinsing procedures should be followed.

2.11.2 Reducing Body Burden

The total body burden of toluene is reduced by measures that increase the rate of metabolism and excretion. Oxygen therapy and positive-pressure ventilation have been used as emergency treatments following episodes of toluene abuse (Graham 1990). This procedure promotes the loss of unmetabolized toluene from the lungs. Increased oxygen availability also has a positive effect on the rate of oxidative metabolism in the liver, lungs, intestines, and other tissues.

Increased fluid consumption, which increases the rate of urine production and excretion, will help to decrease the toluene body burden since toluene metabolites are water soluble and excreted in the urine. In cases where kidney function has been impaired, renal dialysis has been used to remove toluene metabolites from the body (Graham 1990).

2.11.3 Interfering with the Mechanism of Action for Toxic Effects

In cases where toluene has caused cardiac arrhythmias, antiarrhythmic medications have been used to control the heart beat (Graham 1990). No other medical practices for ameliorating the toxic effects of toluene were identified in the available literature. When toluene exposures are unavoidable, as in the workplace, avoidance of alcohol or medications that may inhibit metabolic disposition of toluene is another measure that can be taken to reduce health risks from exposure.

2.12 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 toluene 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 toluene.

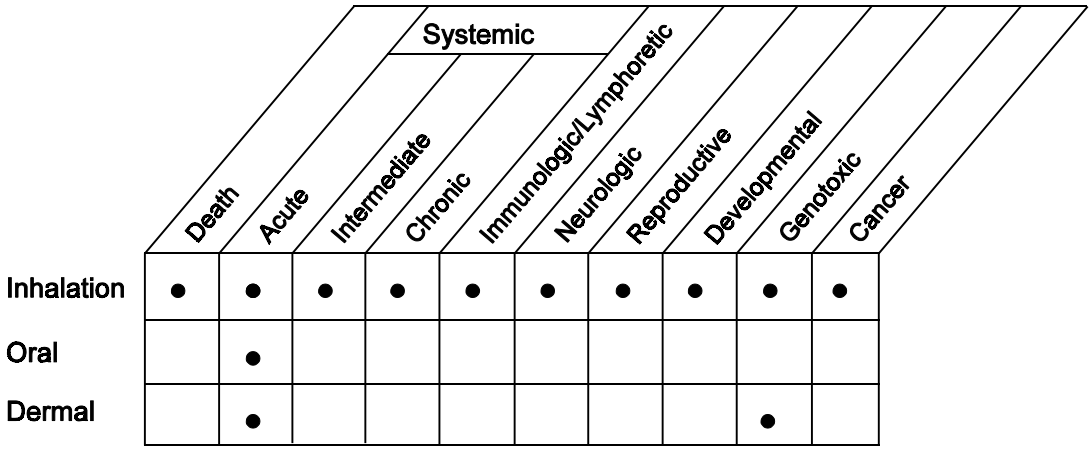
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

2.12.1 Existing Information on Health Effects of Toluene

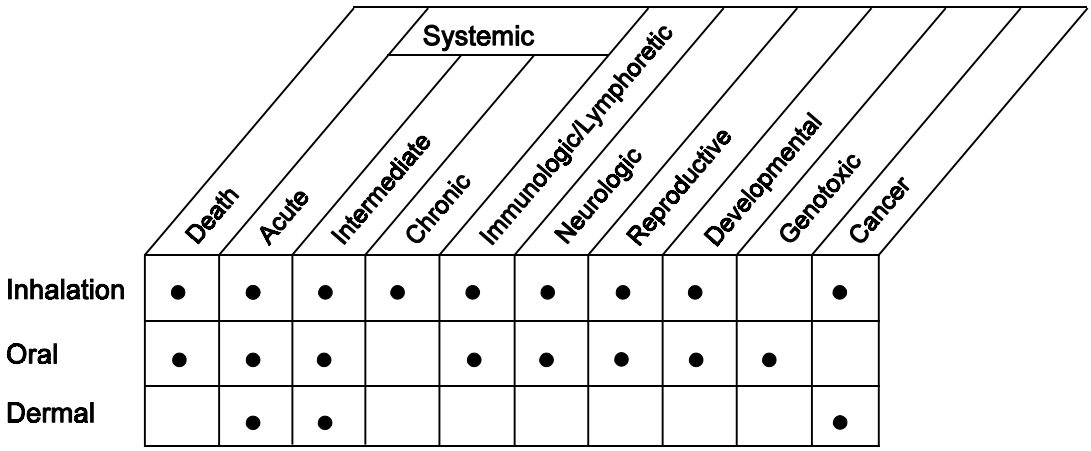
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to toluene are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of toluene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 2-5, there is a considerable body of data on the health effects of toluene in humans following acute, intermediate, and chronic inhalation exposures. It appears that clinical effects of high concentrations on the major target organ, the central nervous system, have been well characterized. However, many of the available reports lack quantitative information on exposure levels and there is still much that must be learned about the ultra structural molecular level of toxicity. There are some oral, but essentially no dermal, data available; however, these are not primary routes by which humans are exposed

Figure 2-5. Existing Information on Health Effects of Toluene



Human



Animal

● Existing Studies

to toluene. Figure 2-5 also shows that considerable animal toxicity data for inhalation exposure are available. However, there are limited oral and dermal data from animal studies.

2.12.2 Identification of Data Needs

Acute-Duration Exposure. Several studies are available regarding the effects of single exposures to toluene, both in humans and animals (Andersen et al. 1983; Baelum et al. 1985; Echeverria et al. 1991; von Oettingen et al. 1942). These studies clearly identify the nervous system as the critical toxicity target of toluene, and describe dose-response relationships between neurological end points and exposure levels. Supporting data are provided by studies of animals after inhalation (Bowen and Balster 1998; Bruckner and Peterson 1981a, 1981b; Bushnell et al. 1985; Hinman 1987; Kishi et al. 1988; Mullin and Krivanek 1982; Taylor and Evans 1985; Wood et al. 1983) or oral (Dyer et al. 1988) exposure. Further studies of orally-exposed animals involving a range of exposure levels (including low levels) and employing sensitive, behavioral, ultra structural, and biochemical measurements may be useful. Data for the dermal exposure route are limited; however, this is not a primary route of human exposure. Sufficient data for the oral and inhalation routes were available to derive an acute inhalation MRL based on a lack of neurological effects in volunteers exposed to 40 ppm toluene for 6 hours (Anderson et al. 1983) and an acute oral MRL based on changes in flash-evoked brain potentials observed in mice exposed to 250 mg/kg toluene (Dyer et al. 1988).

Intermediate-Duration Exposure. Several studies are available on repeated-dose exposure of humans and animals to toluene after inhalation exposure (Bjornaes and Naalsund 1988; Kyrklund et al. 1987; Mattsson et al. 1990; Pryor 1991; von Oettingen et al. 1942). These studies have elucidated the effects of repeated exposure of toluene on the primary target organ, the central nervous system. No-effect levels for intermediate, low-level inhalation exposure in air have not been thoroughly investigated. Determination of these values would be valuable in evaluating the human health risk. Studies on repeated intermediate-duration exposure of humans and animals to toluene by the oral route are adequate (Hsieh et al. 1989, 1990b; Kostas and Hotchin 1981; NTP 1990), and sufficient data were available to derive an intermediate-duration oral MRL based on toluene-induced changes in brain levels of biogenic monoamines in mice (Hsieh et al. 1990b). Studies following dermal exposure are lacking, however, this is not a primary route by which humans are exposed to toluene.

Chronic-Duration Exposure and Cancer. Numerous case reports have associated chronic inhalation exposure to toluene at levels inducing narcosis and euphoria (4,000 to 12,000 ppm as estimated by Gospe et al. 1994) with persistent neurological damage (Byrne et al. 1991; Caldemeyer et al. 1996; Devathasan et al. 1984; Filley et al. 1990; Hunnewell and Miller 1998; Ikeda and Tsukagoshi 1990; Kamran and Bakshi 1998; King et al. 1981; Maas et al. 1991; Meulenbelt et al. 1990; Miyagi et al. 1999; Rosenberg et al. 1988a, 1988b; Ryu et al. 1998; Suzuki et al. 1983; Yamanouchi et al. 1995). Studies of workers repeatedly exposed to toluene in workplace air at concentrations ranging from about 30 to 150 ppm have found evidence for increased incidence of self-reported neurological symptoms (Orbaek and Nise 1989; Yin et al. 1987), performance deficits in neurobehavioral tests (Boey et al. 1997; Foo et al. 1990; Orbaek and Nise 1989), hearing loss (Abbate et al. 1993; Morata et al. 1997), changes in visual-evoked brainstem potentials (Vrca et al. 1995, 1997a, 1997b), and color vision impairment (Zavalic et al. 1998a, 1998b, 1998c). Two animal studies have investigated the effects of toluene following chronic inhalation exposure (CIIT 1980; NTP 1990). Multiple end points of toxicity were investigated, including carcinogenicity, and the data indicate that toluene is not a carcinogen. Sufficient data for the inhalation route were available to derive a chronic MRL based on color vision impairment in toluene exposed workers (Zavalic et al. 1998a). Additional prospective studies of hearing, color vision ability, and performance in neurobehavioral tests of groups of occupationally exposed workers may decrease uncertainty in the chronic inhalation MRL for toluene. The chronic effects of toluene have not been investigated following oral or dermal exposures, and the carcinogenic potential has not been studied following dermal exposure; however, these are not considered major routes of toluene exposure.

Genotoxicity. To evaluate the potential of toluene to cause chromosomal damage, well designed *in vivo* studies using test material of known purity may be valuable. These tests would aid in determining whether toluene itself has clastogenic potential or whether the positive results that have been reported are due to impurities in the test material (animal studies) or multiple solvent exposures (human studies) (API 1981; Bauchinger et al. 1982; Nise et al. 1991; Pelclova et al. 1990; Schmid et al. 1985). Because it is believed that toluene toxicity may be mediated, at least in part, through a highly reactive and short-lived arene oxide intermediate, which interacts with cellular proteins and RNA (Chapman et al. 1990), further studies of this interaction would provide useful information.

Reproductive Toxicity. In general, available results from studies of toluene-exposed workers and animals suggest that toluene is not a potent reproductive toxicant, but may cause some reproductive problems, especially with repeated inhalation exposure during pregnancy to concentrations above 200 ppm. There are a few reports that women occupationally exposed to toluene, or wives of men

similarly exposed, have an increased risk of spontaneous abortions (Lindbohm et al. 1992; Ng et al. 1992b; Taskinen et al. 1989), but a causal relationship is not established by these studies due to small sample sizes evaluated, inability to define accurate exposure levels, failure to account for potentially important confounding variables, and difficulty in validating self-reported data. In addition, one study reported that toluene-exposed male workers showed decreasing plasma levels of the luteinizing hormone, follicle stimulating hormone and testosterone levels with increasing concentrations of toluene (8–<111 ppm) (Svensson et al. 1992a, 1992b). Animal studies found some evidence for minor toluene-induced changes in male and female reproductive organs (Ono et al. 1995, 1996; Tap et al. 1996), but no histological evidence of structural damage to the reproductive organs in rats and mice exposed orally for intermediate durations or by inhalation for intermediate or chronic durations (NTP 1990). No evidence for impaired reproductive performance was found in several assays (API 1985; Smith 1983; Ono et al. 1995, 1996; Thiel and Chahoud 1997) (including a 2-generation study of rats exposed to up to 2,000 ppm, 6 hours/day [API 1985]), except that exposure to concentrations above 200 ppm during pregnancy produced increased fetal mortality in pregnant rats (2,000 ppm, 6 hours/day) (Ono et al. 1995, 1996) and increased abortions in pregnant rabbits (267 ppm, 24 hours/day) (Ungvary and Tatrai 1985). Additional studies of reproductive end points in groups of occupationally exposed workers may be useful in discerning the possible reproductive hazards of toluene in the workplace, if large enough groups of workers are examined, exposure levels can be accurately monitored, and confounding variables are accounted for or minimalized. Another 2-generation reproductive study in another animal species (e.g., rabbits) may also help to decrease uncertainty in defining no-effect levels for reproductive effects from toluene.

Developmental Toxicity. Published reports of birth defects described in children born to women who abused toluene or other organic solvents during pregnancy suggest that high-level exposure to toluene during pregnancy can be toxic to the developing fetus (Arnold et al. 1994; Erramouspe et al. 1996; Goodwin 1988; Hersch 1988; Hersch et al. 1985; Lindemann 1991; Pearson et al. 1994). Studies of developmentally toxic effects in children of women exposed during pregnancy to much lower concentrations are restricted to a small study of 14 Finnish women exposed to mixed solvents suggesting that solvent exposure may increase risk for central nervous system anomalies and neural tube closure defects (Holmberg 1979). The available human data do not establish causality between low-level or occupational exposure to toluene and birth defects, because of the small sample size and the mixed solvent exposure experienced by the subjects in the Holmberg (1979) study and the lack of other studies of possible birth defects in children of women exposed to toluene in the workplace. Additional studies of

developmental end points in offspring of mothers exposed to toluene in the workplace may help to clarify the potential for human health risk.

Results from several inhalation exposure studies of animals indicate that exposure to levels of toluene that begin to produce maternal toxicity can cause fetal effects, including reduced fetal survival and retardation of growth and skeletal development (Courtney et al. 1986; Hudak and Ungvary 1978; Huntingdon Research Centre 1992a, 1992b; Ono et al. 1995; Thiel and Chahoud 1997; Ungvary and Tatrai 1985). No-effect levels in animals for toluene effects on standard developmental end points range from about 133 ppm for a 24 hour/day exposure protocol (Ungvary and Tatrai 1985) to 133–750 ppm with 3–6 hours/day protocols (Huntingdon Research Centre 1992b; Klimisch et al. 1992; Thiel and Chahoud 1997; Ungvary and Tatrai 1985). In animal studies of oral exposure during gestation, no developmental effects were observed in pregnant mice exposed to oral doses of 1,800 or 2,350 mg/kg/day (Seidenberg et al. 1986; Smith 1983), but exposure of pregnant rats to gavage doses of 650 mg/kg /day produced offspring with decreased body weights, delayed ossification, smaller brain volumes, and decreased forebrain myelination per cell compared with controls (Gospe and Zhou 1998; Gospe et al. 1996).

Results from studies of neurobehavioral end points in rats following *in utero* exposure to toluene suggest that maternal exposure to airborne concentrations above 1,200 ppm, 6 hours/day gestation can impair behavioral development of rat offspring (Jones and Balster 1997; Ono et al. 1995; Thiel and Chahoud 1997) and that drinking water exposure during gestation and lactation at doses of 106 mg/kg/day changes postweaning open-field locomotor activity in rat offspring (Kostas and Hotchin 1981).

Additional studies of sensitive neurological end points, including neurobehavioral end points, in offspring of toluene-exposed pregnant animals may better determine no-effect levels for toluene effects on neurodevelopment. Inhalation exposure studies are likely to be of more relevance to human exposures of concern than oral exposure studies. Developmental effects have not been investigated following dermal exposure; however, this is not a primary route of human exposure.

Immunotoxicity. The only inhalation data available on possible immunological effects of toluene are from studies of exposed workers (Lange et al. 1973; Moszczynsky and Lisiewicz 1984; Yin et al. 1987). In all cases, the workers were exposed to several solvents (toluene, benzene, and xylene), thus making it difficult to associate the effects on the immune system specifically with toluene. Animal data using the oral route of exposure provide some evidence of immunotoxicity from toluene exposure (Hsieh et al. 1989). Accordingly, oral and inhalation studies in animals designed to clarify the effect of toluene on the

immune system, particularly on lymphocyte production and function, antibodies, and interferons, may help determine if toluene was involved in the effects on immunity observed in occupationally exposed workers. Additional studies of the impact of toluene on disease resistance, building on the work of Aranyi et al. (1985), may also be valuable.

Neurotoxicity. Effects on the human nervous system from inhalation exposure to toluene are well documented (Andersen et al. 1983; Baelum et al. 1985; Byrne et al. 1991; Devathasan et al. 1984; Echeverria et al. 1991; Filley et al. 1990; Foo et al. 1990; Hanninen et al. 1976; Ikeda and Tsukagoshi 1990; Orbaek and Nise 1989; Rosenberg et al. 1988a, 1988b; Vrca et al. 1995, 1996, 1997a, 1997b; Zavalic et al. 1998a, 1998b, 1998c) and are the basis for the inhalation exposure MRLs. The central nervous system effects of toluene in animals have also been studied in detail via the inhalation route of exposure (Arito et al. 1988; Bruckner and Peterson 1981a; Bushnell et al. 1985; Hinman 1987; Ikeda et al. 1986; Mattsson et al. 1990; Pryor 1991; Pryor et al. 1991; Rebert et al. 1989a; Taylor and Evans 1985; Wood and Colotla 1990). Available data clearly indicate that the central nervous system is a target, but the molecular mechanisms of toxicity have yet to be elucidated with certainty. Dose-response relationships for central nervous system effects in humans and animals (rats and mice) have been established, but more information concerning the reversibility of effects (especially when exposure is chronic) may be useful. The effects of toluene on neurobehavioral function were used to derive an MRL of 4 ppm for acute inhalation exposure (based on a study by Andersen et al. 1983) and a chronic-duration MRL of 1 ppm (based on a study by Zavalic et al. 1998a). Additional studies concerning the progression of subtle, toluene-induced nervous system defects, such as diminished auditory responses, changes in flash evoked visual responses, and impaired color vision discrimination, may decrease uncertainties in the MRLs.

The neurological effects of toluene via the oral route have not been extensively investigated, but the available data support the inhalation data in identifying the nervous system as the critical target of toluene toxicity. An acute MRL of 0.8 mg/kg/day was developed based on a change in flash-evoked potential waveforms in rats exposed to a single dose of toluene (Dyer et al. 1988). The intermediate-duration MRL (0.02 mg/kg/day) was based on a regional increase in the levels of selected neurotransmitters in the brains of exposed mice (Hsieh et al. 1990b). Additional studies may help define the functional manifestation of regional alterations in levels of neurotransmitters in the brain and of changes in FEP waveforms. No data on dermal exposure are available, but this is not the primary route of human exposure.

Epidemiological and Human Dosimetry Studies. Additional studies of neurological and reproductive end points in groups of toluene-exposed workers may decrease uncertainty in the chronic MRL and may help determine if toluene represents a reproductive health hazard in humans at low exposure levels. These studies will be most useful if groups of workers can be identified whose exposure to other chemicals in the workplace is minimal, if adjustments for lifestyle confounding factors can be made, and if personal air monitoring data are available. Earlier reports of increased risk of spontaneous abortions (Lindbohm et al. 1992; Ng et al. 1992b; Taskinen et al. 1989) and altered plasma levels of male sexual hormones (Svensson et al. 1992a, 1992b) in groups of toluene-exposed workers await confirmation from further research.

Biomarkers of Exposure and Effect.

Exposure. Toluene and its metabolites are easily detected in the blood and urine (DeRosa et al. 1985; Hjelm et al. 1988; Kono et al. 1985; Lof et al. 1990; Ogata et al. 1970). However, many toluene metabolites are also produced by other naturally occurring or xenobiotic materials and, thus, are not specific for toluene. The presence of toluene in exhaled air and blood is the most reliable biomarker of exposure (Foo et al. 1991; Kawai et al. 1992a). The ACGIH (1999) recommends using a combination of three biological exposure indices to assess exposure of workers to toluene in the workplace: *ortho*-cresol and hippuric acid levels in urine at the end of a workshift and toluene levels in blood immediately prior to the last shift of a workweek.

Angerer et al. (1998a) proposed that S-*p*-toluylmercapturic acid levels in urine may also be useful as a biological indicator of toluene exposure. Maestri et al. (1997) reported that end-of-shift levels of S-benzylmercapturic acid in urine of workers were correlated with toluene concentrations with a coefficient of 0.74. Additional studies may help determine whether these are reliable biomarkers of exposure that can improve the accuracy of monitoring workers' exposure to toluene.

Effect. There are no suitable biomarkers of effect except for changes in the brain found in chronic solvent abusers with obvious neurological dysfunction (Filley et al. 1990; Rosenberg et al. 1988a). Additional information on the mechanism of neurotoxicity may suggest a useful biomarker of either exposure or effect. However, at this time, there is little to suggest that such biomarkers are present for anything other than the abuse paradigm.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of toluene in humans and animals following inhalation exposure are well characterized (Ameno et al. 1992; Andersen et al. 1983; Angerer 1979; Angerer et al. 1998a; Baelum et al. 1987, 1993; Benignus et al. 1981; Benoit et al. 1985; Bergman 1979; Bray et al. 1949; Carlsson 1982; Carlsson and Ljungquist 1982; Chand and Clausen 1982; Dossing et al. 1983c; Furman et al. 1998; Ghantous and Danielsson 1986; Hjelm et al. 1988; Ikeda et al. 1990; Kawai et al. 1992a, 1992b, 1993, 1996; Lof et al. 1990a, 1990b, 1993; Maestri et al. 1997; Nakajima and Wang 1994; Nakajima et al. 1991, 1992a, 1992b, 1993, 1997; Ng et al. 1990; Ogata 1984; Pellizzari et al. 1992; Pierce et al. 1996, 1999; Paterson and Sarvesvaran 1983; Takeichi et al. 1986; Tassaneeyakul et al. 1996; Van Doorn et al. 1980; Wang and Nakajima 1992; Zahlsen et al. 1992).

Sufficient pharmacokinetic data have been generated to support the development of PBPK models that describe the kinetics of toluene after inhalation exposure; two for humans (Fisher et al. 1997; Pierce et al. 1996, 1999) and two for rats (DeJongh and Blaauboer 1996, 1997; Tardif et al. 1993). Further development of a human PBPK model that includes partitioning of inhaled and ingested toluene to the brain and a similarly designed rat PBPK model may be useful in improving extrapolation from the oral exposure rat data and in comparing model-based predictions of human effect levels based on neurological effects in inhalationally-exposed rats with observed effect levels in humans exposed to airborne toluene. Additional studies of the appearance and elimination kinetics of toluene in breast milk may help to validate the human PBPK model developed by Fisher et al. (1997) to estimate transfer of toluene to a nursing infant. It is unlikely that such studies would be done with volunteers, but studies of nursing animals may provide pertinent information if a similar rat PBPK was developed.

Limited data are available on the quantitative absorption and excretion of toluene by the oral and dermal routes. Studies of humans and animals indicate that dermal absorption of toluene is slow (Aitio et al. 1984; Dutkiewicz and Tyras 1968), but can be significant (Aitio et al. 1984; Monster et al. 1993; Morgan et al. 1991; Sato and Nakajima 1978). Additional studies of dermal uptake of toluene from solution may help to further quantify exposure by this pathway.

Comparative Toxicokinetics. Available data suggest that there are species, age, gender, and strain differences in the metabolism of toluene (Chapman et al. 1990; Inoue et al. 1984, 1986; Nakajima et al. 1992b). Further evaluation of these differences, and comparison of metabolic patterns in humans with those of animals, may help determine the most appropriate species and strain of animal to use in

evaluating the risk of human exposure to toluene. Additional evaluation of human variability in disposition of toluene is also warranted.

Methods for Reducing Toxic Effects. Oxygen therapy and positive pressure ventilation have been used to reduce the toluene body burden (Graham 1990). Washing of toluene from exposed body surfaces is beneficial. Other than these general guidelines, there is very little information available on methods of mitigating the toxic effects of toluene. Additional data on the outcome of emergency response procedures would be beneficial. Studies of the benefit of diet, ethanol absence, and controlled exposure to prescription or nonprescription drugs on blood levels of toluene and its metabolites could provide information that would be helpful in understanding the impact of these factors on the risks from occupational exposure.

Children's Susceptibility. The effects of toluene have not been thoroughly studied in children or immature animals, but the effects observed in juvenile toluene abusers (Byrne et al. 1991; Devasthasan et al. 1984; King et al. 1981) and immature animals exposed to toluene (Castilla-Serna et al. 1991; Pryor and Rebert 1992; Pryor et al. 1984a; von Euler et al. 1989b) are consistent with effects observed in adults. Information regarding age-related differences in toluene metabolism suggests that developing fetuses and children at very early stages of development may be more susceptible to toluene toxicity than adults due to lower capabilities to metabolically detoxify toluene, but, by 1–3 years of age, adult capabilities may be attained (Leeder and Kearns 1997; Nakajima et al. 1992b, 1997; Tassaneeyakul et al. 1996; Vieira et al. 1996). An oral lethality study in rats (Kimura et al. 1971) and a study of toluene-induced hearing loss in young rats (Pryor et al. 1984a) provide the only health effect data suggesting that immature animals may be more susceptible than adult animals. Additional research on the development of metabolic capabilities in newborn and very young children, coupled with animal studies examining relevant neurological end points in toluene-exposed animals of varying ages, may lead to better understanding of the susceptibility of children to toluene toxicity.

Studies with pregnant mice suggest that distribution of inhaled toluene to fetal tissue is limited due to maternal metabolic detoxification and preferential distribution of nonmetabolized toluene to maternal adipose tissue (Ghantous and Danielsson 1986). 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.

Transfer of toluene to infants from breast milk of nursing mothers who are concurrently exposed to toluene in the workplace is expected to be a possibility and a concern (see Section 2.7). As discussed in the Absorption, Distribution, Metabolism, and Excretion subsection above, additional studies of the kinetics of elimination of toluene from nursing animals may provide pertinent information to better predict the degree to which toluene may be transferred in breast milk from a toluene-exposed working mother to her nursing infant. Monitoring studies of toluene in breast milk in groups of toluene-exposed lactating women may also provide some pertinent information.

2.12.3 Ongoing Studies

There are several ongoing research efforts that will provide data related to the toxic actions of toluene (FEDRIP 1998). These projects are summarized in Table 2-6. Some of this research will supply information identified in the preceding section on research needs. Three of the investigators are studying the effects of toluene in humans, focusing on different end points. Dr. M. Utell of the University of Rochester is studying the effects of toluene on neurological and respiratory end points in humans, while Dr. E. Faustman of the University of Washington is examining the effects of toluene on the endocrine system. Dr. D.M. Christiani of Harvard University is assessing the reproductive outcomes of occupational exposure to aromatic solvents, including toluene, in the oil refinery system in China.

Two investigators are using animal models to study the effects of toluene. Dr. R. Balster of Virginia Commonwealth University is investigating the abuse of inhalants, including toluene, using behavioral test procedures in mice. D.N. Kurtzman of Texas Tech University is investigating the relationship between ATPase activity and tubular function in rat and rabbit kidneys.

Table 2-6. Ongoing Research for Toluene

Investigator	Affiliation	Research description	Sponsor
Backes, W	Louisiana State University Medical Center, New Orleans, LA	Toxicological significance of alkylbenzene metabolism	National Institute of Environmental Health Sciences
Balster, RL	Virginia Commonwealth University, Richmond, VA	Behavioral pharmacology of abused solvents	National Institute on Drug Abuse
Branch, S	North Carolina State University, Raleigh, NC	DNA methylation effects on mammalian development	National Institute of Environmental Health Sciences
Christiani, DM	Harvard University	Reproductive outcomes of occupational exposure to aromatic solvents in the oil refinery system in China	
Cunningham, ML	National Institute of Environmental Health Sciences, Research Triangle Park, NC	Metabolism and genotoxicity of genotoxic noncarcinogens	National Institute of Environmental Health Sciences
Faustman, EM	University of Washington, Seattle, WA	Human reproductive endocrine effects of solvent exposure	National Institute for Occupational Safety and Health
Fechter, LD	University of Oklahoma Health Science Center, OK	Mechanisms of organic solvent ototoxicity	National Institute of Environmental Health Sciences
Greenberg, A	University of North Carolina, Charlotte, NC	2,3 Eposyoxepins as benzene ring opening metabolities	National Institute of Environmental Health Sciences
Kalman, DA	University of Washington, Seattle, WA	Human dosimetry for assessment of exposure to volatile compounds	National Institute of Environmental Health Sciences
Karol, MH	University of Pittsburgh, Pittsburgh, PA	Chemically induced chronic allergic lung disease	National Institute of Environmental Health Sciences
Kurtzman, DN	Texas Tech University	Relationship between ATPase activity and tubular function in rat and rabbit kidneys	
Lee, L	University of Kentucky, Lexington, KY	Pulmonary afferents in regulation of airway functions	National Heart, Lung, and Blood Institute
Stern, S	University of Rochester, Rochester, NY	Inhalant abuse during gestation	National Institute on Drug Abuse

Table 2-6. Ongoing Research for Toluene *(continued)*

Investigator	Affiliation	Research description	Sponsor
Turtletaub, KW	University of California Berkeley, Berkeley, CA	Protein and DNA adducts following low dose exposure by accelerator, MS	National Institute of Environmental Health Sciences
Utell, M	University of Rochester, Rochester, NY	Effects of toluene on performance in healthy humans	National Center for Research Resources

3. CHEMICAL AND PHYSICAL INFORMATION

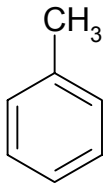
3.1 CHEMICAL IDENTITY

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

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 3-1. Chemical Identity of Toluene

Characteristic	Information	Reference
Chemical name	Toluene	Weast 1989
Synonym(s)	Methylbenzene; phenylmethane; benzene, methyl-; toluol; methylbenzol	Weast 1989; Budavari et al. 1989; RTECS 1998; HSDB 1998
Registered trade name(s)	Methacide	WHO 1985
Chemical formula	$C_6H_5CH_3$	Weast 1989
Chemical structure		EPA 1983b
Identification numbers:		
CAS registry	108-88-3	RTECS 1998
NIOSH RTECS	XS5250000	RTECS 1998
EPA hazardous waste	U220	HSDB 1998
OHM/TADS	7216928	NFPA 1994
DOT/UN/NA/IMCO shipping	UN 1294	HSDB 1998
IMCO	3.2	HSDB 1998
HSDB	131	HSDB 1998
NCI	CO7272	HSDB 1998

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

Table 3-2. Physical and Chemical Properties of Toluene

Property	Information	Reference
Molecular weight	92.14	Weast 1989
Color	Colorless	NFPA 1994
Physical state	Liquid	NFPA 1994
Melting point	-95 EC	Weast 1989
Boiling point	110.6 EC	Weast 1989
Density:		
at 20 EC	0.8669 g/mL	Weast 1989
Vapor density	3.2 (air=1)	HSDB 1999
Odor	Benzene-like	NFPA 1994
Odor threshold:		
Water	0.04–1 ppm	EPA 1987a
Air	8 ppm	HSDB 1998
Solubility:		
Water at 25 EC	534.8 mg/L	Howard 1990
Organic solvent(s)	Miscible	Budavari et al. 1989
Partition coefficients:		
Log K_{ow}	2.72	Howard 1990
Log K_{oc}	1.57–2.25	Howard 1990
Vapor pressure at 25 EC	28.4 mm/Hg	Howard 1990
Henry's law constant:	5.94×10^{-3} atm-m^3/mol	Howard 1990
Autoignition temperature	480 EC (896 EF)	NFPA 1994
Flashpoint	4 EC (40 EF)	NFPA 1994
Flammability limits	1.2–7.1%	NFPA 1994
Conversion factors ppm (v/v) to mg/m^3 in air (20 EC)	1 ppm=3.75 mg/m^3	NIOSH 1986
Explosive limits	1.3% lower limit	Sax and Lewis 1989

v/v = volume for volume

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

4.1 PRODUCTION

Table 4-1 lists the facilities in each state that manufacture or process toluene, the intended use, and the range of maximum amounts of toluene that are stored on site. There are currently 3,062 facilities that produce or process toluene in the United States. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI97 1999). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

About 11% of the total toluene produced in the United States is isolated by distillation of reformed or pyrolyzed petroleum and coal-tar oil. The remainder is added as a mixture, known as benzene-toluene-xylene (BTX), to gasoline (EPA 1990a). One estimate of domestic 1978 production of both isolated and nonisolated toluene was 3 million metric tons (EPA 1981). Most data available, however, are for isolated toluene. According to the latest available data, the domestic capacity has been estimated at 6 million metric tons (1,774 million gallons) (SRI 1988). There are 41 major U.S. producers of toluene (SRI 1999). Production of isolated toluene in the United States from all sources except for distillers and coke oven operators was estimated at 6.7 billion pounds (927 million gallons) in 1995 (C&EN 1996). As of October 1, 1996, the International Trade Commission ceased to collect or publish annual synthetic organic chemicals data. The National Petroleum Refiners Association, which currently collects such data, does not include toluene on its list of organic chemicals.

Toluene is widely used and is produced by a large number of domestic chemical and petroleum companies. In 1979, there were 201 locations in the United States that produced toluene by catalytic reformation, 9 locations where it was produced by petroleum pyrolysis, and six where toluene was produced from coal tar (IARC 1988). The 10 companies which currently produce or supply toluene in the United States are: BP Amoco Corporation; Chevron Chemical Company; CITGO Petroleum Corporation; Coastal Eagle Point Oil Co., Coastal Refining and Marketing, Inc.; Dow Chemical U.S.A.; Equilon Enterprises LLC; Equistar Chemicals LP; Exxon Chemical Company; Fina Oil and Chemical Company, Hovensa, LLC.; Koch Petroleum Group LP; Lyondell-Citgo Refining Company Ltd.; Marathon Ashland Chemical, Inc.; Mobil Chemical Company; Phillips Petroleum Company; Shell Chemical Company; Sunoco, Inc.; Ultramar Diamond Shamrock Corporation; and Valero Energy Corporation(SRI 1999).

Table 4-1. Facilities that Manufacture or Process Toluene

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
AK	2	1,000,000–49,999,999	1, 3, 4, 8
AL	75	0–999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AR	59	0–9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13
AZ	9	0–999,999	8, 9, 10, 11, 12, 13
CA	125	100–99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	22	100–49,999,999	1, 4, 5, 6, 8, 10, 11, 12, 13
CT	33	1000–9,999,999	8, 9, 11, 12, 13
DE	10	1,000–49,999,999	1, 3, 8, 9, 11, 12, 13
FL	47	100–9,999,999	2,3, 8, 9, 10, 11, 12, 13
GA	79	100–49,999,999	1, 2, 3, 6, 8, 9, 10, 11, 12, 13
HI	2	1,000,000–9,999,999	1, 2, 6, 8
IA	51	0–9,999,999	1, 2, 3, 4,7, 8, 9, 10, 11, 12, 13
ID	3	1000–99,999	2, 3, 8, 10,11, 12
IL	198	0–99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	171	100–999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	51	0–999,999,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
KY	57	100–49,999,999	1, 2, 3, 4, 5, 6,7, 8, 9, 10, 11, 12, 13
LA	75	0–999,999,999	1, 2, 3, 4, 5, 6, 7 ,8, 9, 10, 11, 12, 13
MA	74	0–999,999	1, 3, 8, 9, 10, 11, 12, 13
MD	20	1,000–999,999	2, 3, 4, 7, 8, 9, 10, 11, 12, 13
ME	7	100–999,999	1, 2, 3, 6, 8, 11, 12, 13
MI	150	0–49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
MN	65	0–99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MO	81	100–9,999,999	2, 3, 4, 7, 8, 9, 10, 11, 12, 13
MS	61	0–49,999,999	1, 2, 3, 6, 7, 8, 9, 11, 12, 13
MT	6	1,000–49,999,999	1, 3, 4, 6, 7, 8, 9, 13
NC	156	0–999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
ND	3	100–9,999,999	1, 2, 3, 4, 7, 9, 11, 13
NE	19	100–99,999	2, 3, 8,10, 11, 12, 13

Table 4-1. Facilities that Manufacture or Process Toluene *(continued)*

State[a]	Number of Facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
NH	12	100–999,999	8, 11, 12, 13
NJ	107	100–99,999,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
NM	10	100–9,999,999	1, 3, 4, 6, 7, 8, 9, 12, 13
NV	2	1,000,000–9,999,999	9
NY	87	0–9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	203	0–99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	36	1000–49,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
OR	32	0–9,999,999	2, 3, 8, 9, 10, 11, 12, 13
PA	148	0–99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	28	1,000–10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
RI	16	100–999,999	8, 10, 11, 12, 13
SC	63	0–9,999,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13
SD	10	100–99,999	2, 3, 8, 9, 11, 12, 13
TN	115	100–49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
TX	208	100–999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	22	100–49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
VA	83	100–9,999,999	1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13
VI	1	100,000,000–999,999,999	1, 2, 3, 4, 7, 8
VT	6	1,000–99,999	8, 11, 12, 13
WA	39	100–99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
WI	94	0–49,999,999	1, 2, 3, 5, 6, 8, 9, 10, 11, 12, 13
WV	21	100–49,999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
WY	8	0–9,999,999	1, 3, 4, 5, 6, 7, 8, 10, 13

Source: TRI97 1999
[a]Post office state abbreviations used
[b]Range represents maximum 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

4.2 IMPORT/EXPORT

United States imports of toluene in 1984 were estimated at 602 million pounds (273,000 metric tons) (U.S. Department of Commerce 1985a). Exports during the same year were estimated at 289 million pounds (131,000 metric tons) (U.S. Department of Commerce 1985b). No data on recent import/export volume for toluene are available.

4.3 USE

All nonisolated toluene is used in a BTX mixture added to gasoline to improve octane ratings (EPA 1990a). Nearly half of the isolated toluene is used to produce benzene (IARC 1988). About one-third of the isolated toluene is used as a solvent in paints, coatings, adhesives, inks, and cleaning agents. A portion of the isolated toluene goes into the production of polymers used to make nylon, plastic soda bottles, and polyurethanes. Toluene is also used as a starting material in the synthesis of trinitrotoluene (TNT). The remainder is used for pharmaceuticals, dyes, nail polish, and the synthesis of organic chemicals (Cosmetic Ingredient Review Panel 1987). Toluene was once used as an anthelminthic agent against roundworms and hookworms (Krinsky 1980).

4.4 DISPOSAL

Toluene is regulated by the Resource Conservation and Recovery Act (RCRA) as a hazardous waste (F005-spent solvents including toluene) and is therefore subject to RCRA regulations (see Chapter 7). These regulations include standards for storage, transport, and disposal of toluene.

Industrial wastes containing spent solvents may not be disposed of on land if extracts of the waste contain more than 0.33 ppm of toluene. Waste waters containing spent solvents may not be land-disposed if they contain greater than 1.12 ppm of toluene (EPA 1994d).

Consumer products containing toluene are typically disposed of in landfills as municipal waste. No information was available on total disposal of toluene to solid waste landfills. There are no data concerning disposal of toluene by municipal incineration. However, high-temperature incineration (>1,600 EF) probably is very efficient for toluene destruction.

In 1996, it was estimated that about 0.6 million pounds (272 metric tons) of waste toluene was disposed of in publicly owned treatment works (POTW) and about 125 million pounds (5,679 metric tons) of waste toluene was transported from production facilities or points of usage for disposal (TRI97 1999).

Toluene is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995j). Disposal of wastes containing toluene is controlled by a number of federal regulations (see Chapter 7).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Large amounts of toluene enter the environment each year, almost entirely as direct releases to the atmosphere. The largest source of toluene release is during the production, transport, and use of gasoline, which contains about 5–7% toluene by weight. Significant quantities are also released in association with the production, use, and disposal of industrial and consumer products that contain toluene. Small amounts are released in industrial waste water discharges and land disposal of sludges and petroleum wastes.

Toluene in the atmosphere is degraded by reaction with hydroxyl radicals, with a typical half-life of approximately 13 hours. Toluene in soil or water rapidly volatilizes to air, and that which remains is subject to microbial degradation. As a consequence of the volatilization and degradation occurring in air, soil, and water, there is little tendency for toluene levels to build up in the environment over time.

The concentrations of toluene in air have been found to be quite low in remote areas, but levels of 1.3–6.6 ppb are common in suburban and urban areas. The automobile emissions are the principal source of toluene in ambient air, with levels fluctuating in proportion to automobile traffic. Toluene is also a common indoor contaminant, and indoor air concentrations are often several times higher (averaging 8 ppb) than outside air. This is likely due to release of toluene from common household products (paints, paint thinners, adhesives, and nail polish in which it is used as a solvent) and from cigarette smoke.

Toluene is occasionally detected in drinking water supplies, but occurrence is not widespread and levels are generally below 3 ppb. In contrast, toluene is a very common contaminant of water and soil in the vicinity of hazardous waste sites, with average concentrations in water of 7–20 ppb, and average concentrations in soil of over 70 ppb.

The most likely pathway by which people may be exposed to toluene is by breathing contaminated air. Since most people spend a large fraction of the day indoors, indoor air levels are likely to be the dominant source. Moreover, indoor levels generally exceed outdoor levels because of volatilization of toluene from household products. Based on a typical concentration of 8 ppb in indoor air, inhalation of air at 20 m^3/day, and absorption of 50% of the inhaled dose of toluene, a typical absorbed dose is about 300 µg/day. Intake from food and water may contribute substantially smaller amounts. By comparison,

smoking may contribute 1,000 µg/day or more. Higher exposure levels might occur for individuals living near a hazardous waste site or an industrial source of toluene emissions, but these exposures can be estimated only on a site-by-site basis.

Toluene exposure may also occur in the workplace, especially in occupations such as printing or painting, where toluene is used as a solvent. A workplace air level of 100 ppm (equivalent to a dose of 3,750 mg/day) has been established by the Occupational Safety and Health Administration (OSHA) as the 8-hour TWA Permissible Exposure Limit (PEL) for toluene (OSHA 1989a). The American Conference of Governmental Industrial Hygienists (ACGIH 1999) recommends an 8-hour TWA concentration of 50 ppm as the Threshold Limit Value for workplace air to protect against central nervous system effects.

Toluene has been identified in at least 959 of the 1,591 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites evaluated for toluene is not known. The frequency of these sites can be seen in Figure 5-1. Of these sites, 959 are located within the United States and none are located in the Commonwealth of Puerto Rico (not shown).

5.2 RELEASES TO THE ENVIRONMENT

According to the Toxics Release Inventory (TRI), in 1997 a total of 114 million pounds (251 million kg) of toluene was released to the environment from 3,118 manufacturing or processing facilities (TRI97 1999). Table 5-1 lists the amounts released from these facilities to air, water, land, and publicly owned treatment works (POTWs). Table 5-1 also shows that less that 1% of the total released was injected deep underground and that about 3.3 million pounds of toluene were transferred off-site (TRI97 1999). The relative proportions of the material transferred off-site that were recycled or entered environmental media are not stated. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Toluene has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 959 of the 1,591 NPL hazardous waste sites (HazDat 2000).

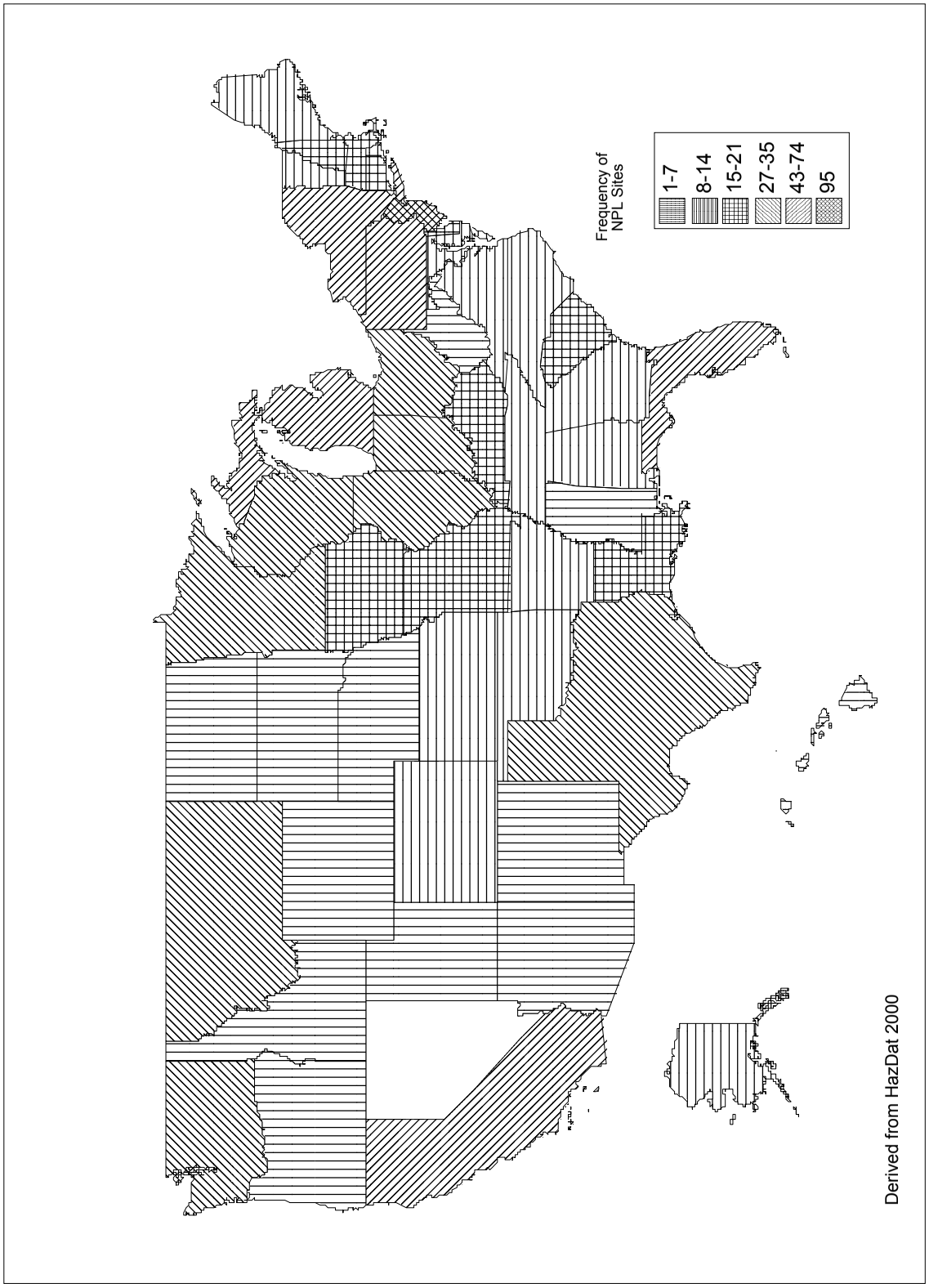


Figure 5-1. Frequency of NPL Sites with Toluene contamination

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Toluene

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
AK	2	88,176	0	265	0	88,441	0	66
AL	75	3,001,377	1,331	0	5	3,002,713	1,046	21,433,270
AR	59	2,209,387	68	3,250	106,107	2,318,812	5	1,755,909
AZ	9	126,923	0	0	0	126,923	0	30,482
CA	125	1,553,654	242	122	500	1,554,518	61,772	13,826,818
CO	22	343,136	0	0	0	343,136	10	2,194,676
CT	33	668,010	5	0	0	668,015	1,155	1,839,393
DE	10	38,727	72	0	0	38,799	50,548	478,664
FL	47	1,429,964	0	3,302	0	1,433,266	899	740,691
GA	79	3,118,819	689	0	0	3,119,508	1,080	5,842,004
HI	2	18,375	0	0	0	18,375	0	2,640
IA	51	1,968,830	66	5	0	1,968,901	9	1,666,065
ID	3	353,942	0	0	0	353,942	0	35,772
IL	198	5,228,891	611	10,252	0	5,239,754	19,136	19,447,474
IN	171	7,710,949	399	33,703	0	7,745,051	2,883	6,933,973
KS	51	1,579,396	307	3,296	420	1,583,419	10	1,885,660
KY	57	5,602,482	613	6,432	0	5,609,527	2,898	6,131,146
LA	75	1,968,292	553	4,120	157,705	2,130,670	0	3,846,996

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Toluene (*continued*)

		Range of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
MA	74	1,625,237	0	7	0	1,625,244	1	7,914,191
MD	20	403,263	3	0	0	403,266	79	2,795,379
ME	7	302,348	0	0	0	302,348	0	87,118
MI	150	6,770,172	387	3,022	6,142	6,779,723	13,541	34,965,822
MN	65	2,235,464	107	0	0	2,235,571	15	2,395,773
MO	81	1,990,918	48	911	0	1,991,877	27,917	23,510,623
MS	61	4,489,512	6,278	421	5,120	4,501,331	254	3,667,812
MT	6	104,600	16	255	0	104,871	5	2,025
NC	156	6,404,347	33	5	0	6,404,385	36,976	6,249,840
ND	3	80,337	0	1	0	80,338	0	28,880
NE	19	776,949	5	0	0	776,954	250	418,576
NH	12	186,830	0	0	0	186,830	5	144,415
NJ	107	1,110,539	85	4,616	0	1,115,240	63,040	14,837,724
NM	10	317,538	0	1,010	0	318,548	0	74,210
NV	2	619,855	0	0	0	619,855	11	137,181
NY	87	4,074,714	575	5	0	4,075,294	5,121	2,204,985
OH	203	3,400,247	3,598	760	0	3,404,605	4,579	18,091,777
OK	36	1,283,992	1,238	439	2,200	1,287,869	726	1,027,209
OR	32	663,051	0	0	0	663,051	171	582,455

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Toluene (*continued*)

		Range of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
PA	148	6,447,689	1,671	251	0	6,449,611	55,637	14,314,073
PR	28	1,130,850	13	0	0	1,130,863	43,141	2,346,775
RI	16	761,923	1	2,089	0	764,013	5	146,233
SC	63	4,931,964	604	1,405	0	4,933,973	510	6,539,868
SD	10	155,429	0	3	0	155,432	0	104,056
TN	115	8,955,221	2,365	0	0	8,957,586	18,460	11,569,814
TX	208	5,519,497	4,899	655,161	235,436	6,414,993	72,065	11,212,189
UT	22	336,598	62	620	0	337,280	9,252	44,622
VA	83	5,191,139	1,020	0	0	5,192,159	116,441	5,728,481
VI	1	151,479	48	0	0	151,527	0	11,934
VT	6	61,159	0	0	0	61,159	250	106,854
WA	39	1,187,149	110	1,480	0	1,188,739	15	823,767
WI	94	2,788,125	0	21	0	2,788,146	2,018	11,500,908
WV	21	1,246,059	2,606	1,429	0–0	1,250,094	0	3,085,704
WY	8	113,513	10	696	0–250	114,219	0	4,610
Totals	**3062**	**112,827,037**	**30,738**	**739,354**	**513,635**	**114,110,764**	**611,936**	**274,767,582**

Source: TRI97 1999

[a]Data in TRI are maximum amounts released by each facility
[b]Post office state abbreviations used
[c]The sum of fugitive and stack releases are included in releases to air by a given facility
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells
POTW = publicly owned treatment works

5.2.1 Air

Nearly all toluene entering the environment is released directly to air. The largest source of emissions is gasoline, which typically contains 5–7% toluene by weight (Verschueren 1977). In 1978, air emissions associated with gasoline use were estimated to be 1.5 billion pounds ($6.8x10^5$ metric tons), the bulk of this ($6.4x10^5$ metric tons) was released through automobile exhaust (EPA 1981). Toluene used in paints, solvents, adhesives, inks, and similar products is also released to air upon use. The total release from these sources not associated with gasoline was estimated to be about $3.7x10^5$ metric tons in 1978 (EPA 1981).

Toluene may also be released during disposal processes. Based on information from 40 medical waste incinerators in the United States and Canada, emission factors for toluene were reported to range from 37.3 to 178 (mean=113) ppb waste for uncontrolled emissions and 177–3,000 (mean=1,920) ppb waste for controlled emissions (Walker and Cooper 1992). Toluene emissions from coal-fired power stations (119 $\mu g/Nm^3$) were reported to be far less than toluene emissions from diesel engines (167–287 $\mu g/Nm^3$) and automobiles (15,700–370,000 $\mu g/Nm^3$, where N denotes 20 EC and 1 atmosphere pressure) (Garcia et al. 1992).

According to the Toxics Release Inventory, in 1997, the estimated releases of toluene of 113 million pounds (249 million kg) to air from 3,118 manufacturing or processing facilities accounted for about 50% of total environmental releases (TRI97 1999). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Toluene has been identified in air samples collected at 187 of the 959 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000).

5.2.2 Water

Toluene may be released to water from industrial discharges and urban wastes, or by spills and leaks of gasoline. However, these releases are believed to comprise only a small fraction of the amount of toluene released to air (EPA 1981). In a survey of toluene levels in industrial waste waters, EPA (1982a) found values ranging from 1 to 2,000 ppb.

According to the Toxics Release Inventory, in 1997, the estimated releases of toluene of 30,378 pounds (166,832 kg) to water from 3,062 manufacturing or processing facilities accounted for about 0.03% of total environmental releases (TRI97 1999). The majority of the releases to water are due to spills of gasoline and oil to surface water (TRI97 1999). Another 611,931 pounds were transferred to POTWs.

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Toluene has been identified in 243 surface water and 1,063 groundwater samples collected from 959 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2000).

5.2.3 Soil

Toluene has been identified in 807 soil and 220 sediment samples collected from 959 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2000).

Release of toluene to land may occur in association with gasoline spills, leaking underground gasoline storage tanks, or land disposal of municipal sludges or refinery wastes. Although, in some cases, releases might be significant on a local scale, the total amount of toluene released to the environment in soil is considered to be negligible (EPA 1981).

According to the Toxics Release Inventory, in 1997, the estimated releases of toluene of 739,354 pounds (1.6 million kg) to soil from 3,062 manufacturing or processing facilities accounted for about 0.65% of total environmental releases (TRI97 1999). Table 5-1 lists amounts released from these facilities. Another 3.3 million pounds were transferred off-site. The TRI data should be used with caution since only certain types of facilities are required to report.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Although toluene is a liquid at room temperature, it is sufficiently volatile (vapor pressure = 28.4 mmHg at 25 EC) that the majority of toluene released to the environment partitions to air. As discussed in Section 5.2, most toluene is released directly into air, and that which is released to surface water or soil

tends to volatilize quickly. The rate of toluene volatilization from surface waters depends on whether the water is static (half-life of 1–16 days) or turbulent (half-life of 5–6 hours) (Mackay and Leinonen 1975; Wakeham et al. 1983). Laboratory studies indicate that surfactants can affect volatilization of toluene from water (Anderson 1992). The rate of volatilization from soils depends on temperature, humidity, and soil type, but under typical conditions, more than 90% of the toluene in the upper soil layer volatilizes to air within 24 hours (Balfour et al. 1984; Thibodeaux and Hwang 1982). Toluene present in deep soil deposits, however, is much less likely to volatilize. Calculations of toluene volatilization for deposits 1–1.3 m below the soil surface suggest that only 0.1–2.6% will volatilize over a 1-year period (Jury et al. 1990). The higher volatilization value allows for a soil water evaporation rate of 0.1 cm/day and the lower value assumes no water evaporation.

Because toluene is moderately soluble in water (534.8 ppm at 25 EC), it is likely that toluene is scrubbed from air by rainfall, but no quantitative estimate of the rate of this transport process was located. Toluene removed from the atmosphere by this process is likely to be rapidly volatilized.

The rate of toluene transport to groundwater depends on the degree of adsorption to soil. The log organic carbon-water partition coefficient is 2.25, which indicates that toluene will be moderately retarded by adsorption to soils rich in organic matter, but will be readily leached from soils with low organic content (Wilson et al. 1981). Soil desorption can be slow. Distilled water removed 9–40% of the toluene adsorbed to samples of five different soils of low organic content within 24 hours (Pavlostathis and Mathavan 1992), but after 7 days some of the toluene still remained adsorbed to the soil samples. Studies of the sorption mechanism when biological activity is minimized show that the primary, or partitioning process, is very fast, but the adsorption process is much slower (Wojtenko et al. 1996). A gravimetric method shows that adsorption of gas phase toluene on loam or clay occurs in two stages: fast diffusion and adsorption in macropores, followed by slower diffusion and adsorption in intragrain micropores (Arocha et al. 1996). Although the organic carbon content of aquifer materials is an important determinant of toluene migration in groundwater, other factors may be important as well (Larsen et al. 1992). For example, information from waste sites and U.S. coastal plain aquifers indicates that many site-specific hydro geologic factors can have unpredictable effects on toluene migration (Adams and Golden 1992). In addition, the presence of other gasoline components (benzene, xylene) can impact toluene migration. Competitive sorption between these gasoline components decreases the interaction between toluene and soil, thereby allowing it to move more quickly through the aquifer (Stuart et al. 1991).

Based on its lipophilic properties, toluene is expected to have a low tendency to bioconcentrate in the fatty tissues of aquatic organisms (Franke et al. 1994). The bioconcentration factor was estimated to be about 10.7 in fish (EPA 1980a) and about 4.2 in mussels. The levels that accumulate in the flesh of aquatic species also depend on the degree to which the species metabolize toluene. The highest tissue levels of toluene tend to occur in species such as eels, crabs, and herring that have a low rate of toluene metabolism (EPA 1981). Metabolism of toluene limits its tendency to biomagnify in the food chain.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Toluene in the atmosphere is rapidly degraded by reaction with hydroxyl radicals to yield cresol and benzaldehyde, which in turn undergo ring cleavage to yield simple hydrocarbons (Davis et al. 1979; Hoshino et al. 1978; Kenley et al. 1973). The estimated rate constant for this process is about $0.6–2.4x10^{-5}$ sec^{-1}, which corresponds to an atmospheric half-life of around 13 hours. The actual half-life may range from 10 to 104 hours depending on atmospheric conditions (Howard et al. 1991). Toluene is also oxidized by reaction with nitrogen dioxide, oxygen, and ozone, but the rates of these reactions are two or more orders of magnitude less than for the hydroxyl radical (Altshuller et al. 1971; Dilling et al. 1976; Wei and Adelman 1969). Benzyl nitrate and nitrotoluene are formed through the reaction of atmospheric toluene with nitrogen oxides (Atkinson 1990). Photolysis is not a significant degradation pathway for toluene (EPA 1981). Smog chamber experiments with hydroxyl radical oxidation of toluene under simulated atmospheric conditions produce numerous carbonyl products.

5.3.2.2 Water

Although toluene may be oxidized in water by reactions similar to those that occur in air, the rates of these reactions in water are very slow (EPA 1979). The half-life for benzene in reaction with aqueous hydroxyl radicals has been estimated to range from 13 to 54 days (Howard et al. 1991). Degradation of toluene in water occurs primarily by microbial action. The rate of biodegradation is a function of many parameters (temperature, duration of microbial acclimation, etc.). The degradation half-life is less than 1 day under favorable conditions (Wakeham et al. 1983). In surface waters, the biodegradation half-life of toluene was estimated to range from 4 to 22 days, whereas the biodegradation half-life of toluene in groundwater was estimated to range from 7 to 28 days (Howard et al. 1991). The biodegradation of toluene in groundwater can be enhanced by the presence of sulfate, nitrate, potassium, and phosphate

(Acton and Barker 1992; Armstrong et al. 1991; Hutchins 1991). Sulfate enhances toluene biodegradation by acting as an alternate electron acceptor (Acton and Barker 1992). The rate of toluene mineralization was estimated to range from 0.032 to 0.055 ppb hour (Armstrong et al. 1991). Rapid biodegradation (over 90% loss within 7 days) occurs in shallow groundwater (Wilson et al. 1983) and in sludge waste water (Davis et al. 1981). *In-situ* degradation is the most important sink for toluene in contaminated streams. Dilution, volatilization, and biodegradation account for 8, 26, and 66% of toluene loss in a small stream in Massachusetts (Kim et al. 1995). Laboratory studies of *in-situ* toluene biodegradation show results comparable to the stream studies and indicate that the streambed surfaces (sediments and rocks) are responsible for virtually all biodegradation (Cohen et al. 1995). Reduced, but still considerable, rates of toluene microbial degradation were reported in salt water, as compared to fresh water (Price et al. 1974). Bacteria are unable to degrade toluene in water when toluene concentration falls below a threshold value were the metabolism of the compound is too slow to provide cells with energy at a rate needed to maintain metabolism (Roch and Alexander 1997).

5.3.2.3 Sediment and Soil

Toluene can be degraded in soil by a number of bacterial species of the genera *Pseudomonas* and *Achromobacter* (Fewson 1981). The biodegradation process appears to occur in two phases. The first phase produces benzoic acid and is, in this respect, parallel to the metabolism of toluene by mammalian microsomes. In the second phase, the aromatic ring undergoes metabolic cleavage to produce the Krebs cycle intermediates, which are degraded to carbon dioxide or incorporated into bacterial biomolecules (Harayama et al. 1989). Addition of large numbers of bacterial cells to toluene-contaminated soils may have no benefit if the concentration of toluene is too low for the bacteria to maintain metabolic activity (Roch and Alexander 1997). Toluene degradation rates were proportional to the initial substrate concentration, and these rates reached a maximum at a concentration of 200 ppm (Davis and Madsen 1996). In aerobic soils, oxygen acts as the terminal electron acceptor in degradation of the ring cleavage products. Under anaerobic conditions, nitrogen or sulfate can act as the terminal electron acceptor (Beller et al. 1992a, 1992b; Dolfing et al. 1990; Evans et al. 1991). Under favorable conditions (presence of electron acceptors, nutrients, and oxidizable compounds), laboratory studies show that BTEX (benzene-toluene-ethylbenzene-xylene) compounds (which include toluene) are also degraded by bacteria in anaerobic (Langenhoff et al. 1996) or oxygen-limited environments (Lovley 1997; Olsen et al. 1995). Under sulfate-reducing conditions, less than 10% of the toluene carbon was metabolized to benzylsuccinic acid and benzylfumaric acid, whereas >80% was mineralized to carbon dioxide (Beller et at. 1992a). The half-life for biodegradation in soil under laboratory conditions may be as short as 1 hour

(Claus and Walker 1964), whereas half-lives of 1–7 days are typical in the environment (API 1984). Based on data from the aerobic degradation of toluene in water, the biodegradation half-life of toluene in soils is expected to range from 4 to 22 days (Howard et al. 1991). Soil biodegradation is not impeded by adsorption (Robinson et al. 1990). The wood-degrading, white-rot fungus, *Phanerochaete chrysoporium*, mineralizes 50% of 2 ppm aqueous solutions of toluene or benzene, toluene, ethylbenzene, and xylenes (BTEX) compounds to carbon dioxide within 5 days. Nonlignindytic conditions are favored (Yadav and Reddy 1993).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to toluene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on toluene 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.

5.4.1 Air

The concentration of toluene in air has been measured in a number of studies. Table 5-2 summarizes the average concentration as a function of sampling location (EPA 1988b). Background levels of toluene in remote areas were found to be quite low (0.05 ppb), but levels of 0.27–7.98 ppb were observed in suburban and urban areas. Other studies have reported toluene concentrations of 0.9–70.1 ppb, 0.06–195 ppb, and 2.2–751.5 ppb in rural (Khalil and Rasmussen 1992), urban (Chan et al. 1991b; EPA 1991c; Evans et al. 1992; Kelly et al. 1993), and source dominated air samples (Guldberg 1992; Kelly et al. 1993). There are multiple sources of this atmospheric toluene, with vehicle emissions being a major contributor (Altshuller et al. 1971; EPA 1981; Garcia et al. 1992). The emission rate of toluene from motor vehicle traffic in a Los Angeles roadway tunnel was found to be 748 ppm (Fraser et al. 1998). Concentrations of toluene in air from the inside of vehicles have been reported to range from 0.56 to 42.0 ppb (Chan et al. 1991a; Lawryk and Weisel 1996; Weisel et al. 1992).

High air concentrations of toluene were nearly always found indoors (Lebret et al. 1986; Otson et al. 1983; Wallace et al. 1986). In several studies, indoor (home or office) toluene concentrations ranged from 0.7 to 24.2 ppb due mostly to infiltration from auto emissions (Chan et al. 1991b; Hodgson et al. 1991; Kelly et al. 1993; Michael et al. 1990b; Shields and Weschler 1992). Toluene was among the volatile organic compounds detected in the emissions from sponge rubber carpet cushions (Schaeffer et

Table 5-2. Median Toluene Levels in Ambient Air

Sampling location	Number of samples	Daily mean concentration (ppb)	Concentration ($\mu g/m^3$)
Remote	225	0.049	0.18
Rural	248	0.35	1.3
Suburban	958	0.195	0.731
Urban	2,519	2.883	10.81
Source dominated	104	6.314	23.67
Indoor	101	8.4	31.5
Workplace	80	0.865	3.24
Personal	1,650	0.000	0.000

Adapted from EPA 1988b

al. 1996). Indoor toluene can also originate from household products (paints, thinners, glues, etc.) and smoking. The indoor toluene concentrations in a household with smoking residents were found to be greater than those in a nonsmoking household (Montgomery and Kalman 1989).

Volatilization from contaminated tap water is another source of indoor toluene. Efficiencies of toluene volatilization have been estimated for sources such as the kitchen sink (13–26%), residential washing machines (8.2–99%), residential dishwashers (96–98%), and household showers (61–77%) (Howard and Corsi 1996, 1998; Howard-Reed et al. 1999; Moya et al. 1999). Toluene was found to be emitted at a rate of 40,000 ppb during the charbroiling of hamburger meat over a natural gas fired grill (Schauer et al. 1999a). Higher levels of toluene were detected in indoor air during the spring (4.8 ppb) than in the summer (7.70 ppb) (Mukerjee et al. 1997). Indoor and in-vehicle toluene levels appear to be affected by seasonal changes (Montgomery and Kalman 1989; Weisel et al. 1992).

Shields et al. (1996) compared volatile organic compounds measured in three types of commercial buildings (telecommunication offices, data centers, and administrative offices) across the United States The highest amount of toluene was detected in the data centers with a geometric mean concentration of 2.68 ppb. Geometric mean concentrations of toluene measured in telecommunications offices, administrative offices, and outdoor air were 1.3, 1.5, and 0.7 ppb, respectively. The presence of aromatic compounds was found to be independent of occupant density and was attributed to presence of adhesives, building materials, floor and wall coverings, architectural coatings, and cleaning products.

Very high concentrations of toluene (53.2–38,038 ppb) were detected in gas from municipal landfills in Finland (Assmuth and Kalevi 1992). Toluene can enter nearby homes by diffusion and pressure-driven transport from soil (Hodgson et al. 1988).

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5.4.2 Water

A number of surveys have been conducted to investigate the occurrence of toluene in water. Although there is wide variation from location to location, toluene appears to be a relatively infrequent contaminant of drinking water, especially for systems utilizing groundwater sources. For example, in 2 surveys performed between 1977 and 1981, toluene was detected in only 2 of 289 and 11 of 929 samples, at concentrations ranging from 0.5 to 2.9 ppb (EPA 1981). The frequency of detection of toluene in drinking water drawn from surface water sources was somewhat higher (3 of 97 and 20 of 99, respectively), although concentration ranges were similar (0.1–1.6 ppb). Toluene was detected in less than 20% of the samples of groundwater taken from alluvial aquifers beneath Denver, Colorado, a major urban center, at a maximum concentration of 1 ppb (Bruce and McMahon 1996).

Toluene was found in 60 water samples in 48 private wells in the state of Rhode Island. The total number of wells sampled and the number of samples taken was not provided. The concentrations detected ranged from 1 to 3,500 ppb (RIDH 1989). Characteristics of the well sites, such as proximity to a waste site, were not described. Toluene was detected at concentrations of 6,400 and 6,900 ppb in two groundwater sampling wells at a hazardous waste site (Armstrong et al. 1991).

5.4.3 Sediment and Soil

No studies were located regarding levels of toluene in typical urban, suburban, or rural soils. Toluene has been occasionally detected in sediments of surface waters at concentrations averaging 5 ppb (Staples et al. 1985). Toluene was detected in the sediment of lower Passaic River, New Jersey, in the vicinity of combined sewer overflow outfalls (Iannuzzi et al. 1997). The concentrations ranged from 4.0 to 250 ppb. In the absence of continuous releases from a waste site, it is expected that toluene would not persist for long periods in soil, due to its volatility, susceptibility to biodegradation, and water solubility.

5.4.4 Other Environmental Media

Toluene was detected at average levels of 20 ppb in 23% of 150 samples of aquatic biota recorded in the STORET data base (Staples et al. 1985). The concentration of toluene in commercial foodstuffs has not been thoroughly studied. Although the data are limited, the levels of toluene in food are not likely to be significant (EPA 1981). Toluene was detected in eggs stored in polystyrene containers that contained toluene (Matiella and Hsieh 1991). Cigarette smoke is a significant source of toluene, estimated to be about 80 µg/cigarette (Grob 1965). Toluene was detected in a variety of household items including automotive products, household cleaners/polishes, paint-related products, fabric and leather treatments, lubricants and adhesives (Sack et al. 1992). The levels of toluene in these products varied from 1.8 to 23.3% by weight.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Available data indicate that for the general population, inhalation of toluene is likely to be the main route of exposure. Assuming an average concentration in indoor and outdoor air of 2.12 ppb (EPA 1988b), and assuming inhalation of 20 m^3/day and 50% absorption of inhaled toluene (EPA 1981), the typical dose by this route would be about 300 µg/day. Exposure could be higher near heavily traveled roadways or point sources of toluene, and could also be increased by frequent use of home products containing toluene. For example, in an industry-sponsored study, personal inhalation exposures to toluene during the application of nail lacquers in residences ranged from approximately 1,030 to 2,820 µg/person/day (Curry et al. 1994). The mean toluene levels measured in air during the nail laquer application ranged from 0.85 to 2.45 ppm, while the post-application concentrations ranged from 0.05 to 0.27 ppm. No toluene was detected in air prior to the nail laquer application.

Blood concentrations of toluene have been measured in 604 non-occupationally exposed people in the United States who participated in the Third National Health and Nutrition Examination Survey (NHANES III). Participants were selected on the basis of age, race, gender, and region of residence. Toluene was detected in 75% or more of the blood samples and was present at a mean concentration of 0.52 ppb, a median concentration of 0.28 ppb, a 5th percentile concentration of 0.11 ppb, and a 95th percentile concentration of 1.5 ppb (Ashley et al. 1994). Buckley et al. (1997) compared the amount of toluene detected in the blood samples of residents of the Lower Rio Grande Valley to that detected in the NHANES III study. Toluene was found in 81% of the blood samples. The amount of toluene was found to be lower than that observed in NHANES III, the median concentration being 0.17 ppb.

Cigarette smoking may also significantly increase exposure. Assuming inhalation of about 80–100 µg of toluene per cigarette and 50% absorption (EPA 1981; Grob 1965), smoking one pack per day would contribute an absorbed dose of about 1,000 µg/day.

Toluene is a volatile component of wood smoke. Emission rates of toluene during wood combustion in home heating units have been reported in the range of 0.15–1 g/kg of wood (Larson and Koenig 1994).

Based on average values of toluene in water, exposure by ingestion of contaminated drinking water is likely to be relatively small compared to inhalation. The concentration of toluene in drinking water drawn from surface water sources is 0.15–0.25 ppb (EPA 1981), and daily intake by this route (based on ingestion of 2 L/day) would be approximately 0.3–0.5 µg/day. In a survey of bottled drinking water sold in Canada, only 20 (or 11%) of 182 samples analyzed contained measurable amounts of toluene, with an average concentration of 6.92 ppb and a range of 0.5–63 ppb (Page et al. 1993). Toluene is also known to volatilize from various household sources of water such as the kitchen sink, dishwashers, washing machines, and showers water into air; thus, its presence in tap water may ultimately result in inhalation exposure (Howard and Corsi 1996, 1998; Howard-Reed et al. 1999; Moya et al. 1999).

Exposure to gasoline (which contains toluene) has been estimated for a household using gasoline-contaminated water (Beavers et al. 1996). In this house, $694 ppb of toluene was found in the water, 664 ppb in shower air, and 14.9 ppb in non-shower air. Dermal absorption during shower-related activities accounted for 30% of the total dose. Inhalation during shower-related activities represented 25%. Ingestion represented 30%, and non-shower household inhalation 16%. The authors note that personal habits limit the general applicability of these results (Beavers et al. 1996).

Data are not available to estimate intake of toluene from ingestion of food, but these routes are likely to be minor (EPA 1981). A number of studies have indicated significant accumulations of toluene in products for human consumption. For example, escaping gasoline vapors from internal combustion engines used or stored near olives during the growing, harvesting, storage, and processing steps in the production of virgin olive oil can cause significant contamination of the product with toluene and other hydrocarbons (Biedermann et al. 1996). Significant concentrations of toluene have also been measured in 8 of 10 species of fruit tested in a European study, which showed higher concentrations of toluene in the peel than in the pulp of the fruit (Górna-Binkul et al. 1996). Dermal absorption of toluene is not a significant route of exposure. Uptake of toluene via skin has been estimated to contribute 1–2% of the body burden received following whole body (including inhalation) exposure (Brooke et al. 1998).

Although toluene has been found to be a common contaminant at hazardous waste sites, it is not possible to estimate human exposure levels that might occur near waste sites without detailed site-specific information on concentration values in air, water, and soil, and on human intake of these media. Pathways that might be of significance include inhalation of toluene vapors, ingestion of toluene-contaminated water (surface water and/or groundwater), volatilization and inhalation from contaminated water, and dermal contact with toluene-contaminated soil.

Based on average (0.19–0.7 ppm) and maximum (0.26–2.4 ppm) concentrations of toluene in air at service stations, inhalation exposures of self-serve customers, gas station attendants, and downwind residents were estimated to be 0.057 to 0.49, 38, and 0.062 to 0. 29 ppb/day, respectively (Guldberg 1992). An Alaskan study compared the concentration of toluene in blood before and after pumping of regular and oxygenated gasoline in February (Backer et al. 1997). The median concentration of toluene in blood before pumping gasoline was found to be 0.38 ppb. A greater increase was detected in the blood concentration of toluene after pumping oxygenated gasoline (0.85 ppb) than after pumping regular gasoline (0.74 ppb). Other transportation-related toluene exposure pathways include: inhalation of volatile organic compounds from contaminated air in aircraft cabins (2–135 ppb for toluene) (Dechow et al. 1997), and breathing air in long road tunnels (97–167.6 ppb) (Barrefors 1996).

Toluene exposure may also occur in the work place, especially in the printing industry where toluene is used as a solvent for inks and dyes. Occupational exposure may also occur during paint stripping operations (Vincent et al. 1994). Concentrations of 5–50 ppm are common in the workplace with some values as high as 250 ppm (1,000 mg/m^3) (NCI 1985). Assuming that a worker inhales 10 m^3 of air while on the job, and that 50% of the inhaled toluene is absorbed, a workplace concentration of 53.2 ppm would

correspond to an exposure level of 1,000 mg/day. The toluene burden of rotogravure workers measured with personal monitoring tubes was found to be higher (ranging from 14.9 to 120 ppm, median=60.9 ppm) than the air concentration in the workplace (ranging from 37.5 to 87.2 ppm, median=62.8 ppm) (Hammer et al. 1998). In another study, the blood of rotogravure workers was tested before and after the use of toluene to clean containers for the primary printing colors (Muttray et al. 1999). The concentration of toluene in their blood was found to increase from 0.87 to 4.9 ppm. In addition, dermal exposure might also occur from contact with toluene-containing materials, contributing perhaps 20 mg/use (EPA 1981). Personnel working with various types of fuel may be at a risk of toluene exposure. A Finnish study determined the exposure of gasoline tanker drivers to toluene during loading and delivery to be 0.4–2.9 ppm (Hakkola and Saarinen 1996; Saarinen et al. 1998). The exposure level of aircraft maintenance personnel to toluene in raw JP-8 jet fuel vapor was found to be 6.3±1.6 ppm (Smith et al. 1997).

Art materials, especially painting supplies, represent another potential source for exposure to toluene for people of all ages and to people who spend time near an artist's work area or studio, which for about 50% of professional artists is in the home (McCann 1992). Case reports on acute toluene poisoning of workers installing a parquet floor in Singapore (Tan and Seow 1997) and on excessive exposure to toluene in a wood furniture manufacturing facility in the U.S. (Paulson and Kilens 1996) have also been reported. A group of Dutch carpet-layers using water-based adhesives were exposed to an 8-hour average concentration of toluene in the range of 0.27–76.87 ppm, while carpet-layers using contact adhesives were exposed to an 8-hour average concentration of 4.25–161.2 ppm (Muijser et al. 1996). Measurement data for fire-fighters occupationally exposed to combustion products in three separate building fires indicated they were exposed to an average concentration of 0.23 ppm toluene during the time they were fighting the fires (McDiarmid et al. 1991).

Workplace exposure to toluene and other volatiles is associated with the plastics industry (Socie et al. 1997), emissions from waste waters in municipal sewage treatment plants (Bianchi and Varney 1997), with sculptured nail manicure salons (Hiipakka and Samimi 1987), and with hair salons (Hollund and Moen 1998). Combinations of solvents can enhance the dermal penetration of toluene. Methanol enhances the skin absorption of toluene. Special precautions need to be taken against the skin absorption of toluene when handling paint thinners that contain methanol (Tsuruta 1996).

5.6 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 2.7 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, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, they put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and they spend more time outdoors. Children also are closer to the ground, and they do not have the judgment of adults to avoid hazards (NRC 1993).

Exposures of the embryo or fetus to volatile organic compounds such as toluene may occur if the expectant mother is exposed to high levels that overwhelm maternal protective mechanisms including metabolic detoxification and disposition of toluene and possible preferential distribution of toluene to maternal adipose tissues (see Sections 2.3 and 2.5). A newborn infant may be exposed by breathing contaminated air and through ingestion of mother's milk that can contain small amounts of toluene. Children may be exposed through accidental ingestion of products containing toluene. Older children and adolescents may be exposed to toluene in their jobs or hobbies, or through deliberate solvent abuse by "sniffing." Human epidemiological studies and case reports discussing reproductive and/or developmental toxicity of toluene in humans have been reviewed. Exposure routes included occupational duties and sniffing of paints, paint reducers, and paint thinners (Donald et al. 1991b). Inhalant abuse during pregnancy poses significant risks to the pregnancy and endangers both the mother and the fetus. Solvent abuse of toluene for euphoric effects results in exposure levels that equal of exceed those producing adverse effects in animals.

Transfer of toluene to nursing infants from breast milk of currently exposed mothers is expected to be a possibility because of the lipophilicity of toluene and the relatively high lipid content of breast milk. Mobilization during pregnancy or lactation of stored toluene from pre-conception exposure, however, does not appear to be a major concern because most toluene is rapidly eliminated from the body (see Sections 2.3.4 and 2.7). There is also a risk for an adverse effect on the lactation process itself and the

nutritional content of the milk. Women should be counseled about the effects of workplace exposure while breast-feeding (Byczkowski et al. 1994). A physiologically based pharmacokinetic model (PBPK) has been developed to estimate the amount of chemical that an infant ingests for a given nursing schedule and daily maternal occupational exposure to 50 ppm toluene for 8 hours (Fisher et al. 1997). This PBPK model predicted an ingestion rate of 0.460 mg/day for such an infant.

Young children often play close to the ground and frequently play in dirt, which increases their dermal exposure to toxicants in dust and soil. They also tend to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity. Children may be orally and dermally exposed to toluene present as a contaminant in soil and dust, but toluene is not expected to persist for long periods in soil (in the absence of continuous release) due to its volatility, susceptibility to bacterial degradation, and water solubility. It has been demonstrated that the toluene adsorbed on soil is absorbed by the body (Turkall et al. 1991). Toluene in both aqueous solution and vapor phase has also been shown to be absorbed through the human skin, albeit slowly (Brooke et al. 1998; Dutkiewicz and Tyras 1968; Tsuruta 1989). Toluene has a log organic carbon-water partition coefficient of 2.25, indicating moderate adsorption to soil, especially to soil with high organic matter (Wilson et al. 1981). Most of the toluene present in the upper layers of the soil is volatilized to air within 24 hours (vapor pressure=28.4 mmHg at 25 EC) (Balfour et al. 1984; Thibodeaux and Hwang 1982). The degradation half-life of toluene is 1–7 days in soil (API 1984). Loss of toluene from the soil decreases the potential of dermal and oral exposure to children, but its rapid volatilization results in inhalation being the most likely route of exposure.

Children breathe in more air per kilogram of body weight than an adult. Therefore, a child in the same micro-environment as an adult may be exposed to more toluene from ambient air. Young children are closer to the ground or floor because of their height. The toluene vapors being heavier than air (vapor density=3.14 g/mL) tend to concentrate near the ground. The children, therefore, may be at greater risk of exposure than adults during accidental spills of toluene.

Children may also be exposed to fumes of toluene and other hydrocarbons by working with or playing near sources of gasoline. Children’s exposure also occurs through accidental ingestion and inspiration of the chemicals into the lungs. Asthma, pneumonia, pulmonary damage, and death can result. Most accident victims are one- and two-year olds and are about evenly divided between males and females. Most incidents occur in the children’s homes and the products are in their normal storage areas. Child-resistant packaging is recommended (Journal of Environmental Health 1997). Children are also exposed to higher concentrations of toluene in central urban areas with high traffic density, where children's blood

toluene concentrations are, on average, 56% higher than those of children living in rural areas (Jermann et al. 1989; Raaschou-Nielson et al. 1997).

Children are also exposed through hobbies and art activities involving glues, adhesives, and paints (McCann 1992). Abuse of toluene-containing products among young people by inhalation ("sniffing") is a social and clinical concern (Young 1987).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to toluene (see Section 5.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to toluene. These populations include individuals living in proximity to sites where toluene was produced or sites where toluene was disposed, and individuals living near one of the 959 NPL hazardous waste sites where toluene has been detected in some environmental media (HazDat 2000).

The population most likely to experience high levels of exposure to toluene are workers in the printing industry or other industries employing toluene as a solvent. In addition, workers exposed to gasoline vapors are also likely to have higher than average exposure to toluene. Individuals may also be exposed to high levels at home in association with the use of toluene-containing consumer products. Smokers have a considerably higher exposure to toluene than nonsmokers.

Toluene has been frequently identified as a water contaminant in the proximity of hazardous waste sites. Drinking water sources for populations living near a hazardous waste site containing toluene should be evaluated for toluene. If groundwater wells are contaminated, exposure to toluene can occur when the well-water is used for showering, cleaning, cooking, and drinking purposes. Exposure can also occur through contact with contaminated soil.

A troublesome route of exposure to toluene is through deliberate inhalation of fumes from paint thinners, gasoline, glues contact adhesives, and aromatic solvents. Inhalant abuse can affect pregnancy outcome (Jones and Balster 1998). Inhalant abuse is an urgent health care problem among youth, including American Indians (Young 1987). Contact adhesives often contain toluene, heptane, and methyl ethyl ketone. Although toluene is more toxic than the other ingredients, it evaporates more slowly. Thus the vapors inhaled when "sniffing" such adhesives will contain less toluene and should be less toxic than would be expected from its liquid composition (Midford et al. 1993).

5.8 ADEQUACY OF THE DATABASE

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

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

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of toluene that are needed to evaluate its behavior in the environment are available (Table 3-2). It does not appear that further research in this area is essential.

Production, Import/Export, Use, Release, and Disposal. As of October 1, 1996, the International Trade Commission ceased to collect or publish annual synthetic organic chemicals data. The National Petroleum Refiners Association, which currently collects such data, does not include toluene on its list of organic chemicals. The available production data of toluene are out of date. It is essential that these data be updated regularly to allow a more accurate determination of the potential for human exposure.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. This database, Toxic chemical Release Inventory (TRI), will be updated yearly and should provide a list of industrial production facilities and emissions. Available information appears to be adequate for assessing industrial production and the potential for release of toluene at this time. Additional information concerning home-use products containing toluene and their disposal are needed. Household

hazardous waste disposal programs are in their infancy and there are few data on the amounts of waste processed through these programs.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, became available in May of 1998. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Existing information indicates that volatilization, followed by reaction with hydroxyl radicals in air, is the principal fate process for toluene in the environment (Davis et al. 1979; Hoshino et al. 1978; Howard et al. 1991; Kenley et al. 1973). The rate constants for this process have been established, although further refinements would improve the ability to model the fate of toluene emissions. Although toluene is not a common contaminant in water, it has been found to occur in both groundwater and surface water near waste sites (HazDat 2000). Additional studies on the rate of volatilization, degradation, and transport of toluene in groundwater, surface water, and soils would be useful for assessing potential human exposure near hazardous waste sites.

Considerable data are available concerning the genetics of toluene-degrading microorganisms (Fewson 1981; Harayama et al. 1989), but distinctions need to be made between the activities of microorganisms found naturally in the soil and water, and those that are genetically engineered for use in bioremediation projects. Quantitative characterization of the end products of biodegradation and information concerning this fate would also be helpful.

Bioavailability from Environmental Media. On the basis of the available data, toluene appears to be highly bioavailable when it is released to the environment. Inhalation, oral, and dermal absorption occur due to toluene solubility in the lipid matrix of the cell membrane (Alcorn et al. 1991). Absorption is rapid and virtually complete at low exposure concentrations when exposures are oral or respiratory (Alcorn et al. 1991; Carlsson and Ljungqvist 1982; Hjelm et al. 1988). Adsorption also occurs through contact with the skin (Dutkiewicz and Tyras 1968). Additional research on bioavailability of toluene from the environment does not appear to be needed.

Food Chain Bioaccumulation. Very little information was identified pertaining to the bioaccumulation of toluene in the food chain. Despite its lipid solubility, the bioconcentration factor for toluene is expected to be relatively low due to its rapid metabolism to more polar molecules with a lower affinity for lipids, and it has little tendency to bind to biomolecules. Additional research efforts pertaining to bioaccumulation of toluene would be justified for cold water fish with relatively high fat content and for plants used as a source of vegetable oils. It would be helpful to know if toluene becomes incorporated in the lipid deposits of these organisms. Although there has been little data collected concerning the tendency for toluene to biomagnify in the environment, available data on bioconcentration suggest that research on this topic is not needed.

Exposure Levels in Environmental Media. The concentration of toluene in ambient air and in drinking water has been the subject of numerous studies (Bruce and McMahon 1996; EPA 1981, 1988b, 1991c; HazDat 2000; Kelly et al. 1993; Lebret et al. 1986; Michael et al. 1990b; Montgomery and Kalman 1989; Otson et al. 1983; RIDH 1989), but there is a need to maintain the currency of the data. Further studies on toluene levels in food and soil would be useful, since quantitative data for these media are limited. The potential exists for toluene to be present in human and bovine milk due to its lipid solubility, but studies of exposure through these media were not identified. In view of the observation that the highest levels of toluene likely to be encountered by an average citizen occur in the home, studies that identify the sources of toluene in indoor air would be valuable in reducing or eliminating this pathway of exposure.

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

Exposure Levels in Humans. Data from the Total Exposure Assessment Methodology study (EPA 1987c) provide information on the concentration of toluene in the expired air of humans in relation to levels in the air breathed by the individual. Exposure of the general population to toluene in air has been monitored for a variety of scenarios (Backer et al. 1997; Beavers et al. 1996; Biedermann et al. 1996; Curry et al. 1994; EPA 1981; Grob 1965; Guldeberg 1992; Larson and Koenig 1994; Page et al. 1993). Amounts of toluene volatilizing from the household sources such as the kitchen sink, dishwashers, washing machines, and showers have also been estimated (Howard and Corsi 1996, 1998; Howard-Reed et al. 1999; Moya 1999). Combination of this data with appropriate toxicokinetic models of toluene

absorption, distribution, and excretion in humans would allow for improved estimates of exposure levels in humans. Toluene exposure in the workplace is well documented (Hammer et al. 1998; Hiipakka and Samimi 1987; McCann 1992; McDiarmid et al. 1991; Muijser et al. 1996; Muttray et al. 1999; NCI 1985; Paulson and Kilens 1996; Smith et al. 1997; Tan and Seow 1997; Vincent et al. 1994). Continued monitoring will help to minimize exposure of workers. A study of toluene in human milk of occupationally exposed women may be useful in evaluating the risks to this population of mothers and infants. This information would be useful to assess the desirability of conducting health studies on exposed populations.

Exposures of Children. A study on the usefulness of intervention methods in cases of inhalant abuse by pregnant women may help to develop better means of preventing high-level exposure to toluene and other solvents. More research is needed to rule out concomitant risk factors and to identify specific chemicals and patterns of use associated with adverse effects.

Children may be at a greater risk of inhalation exposure to toluene as they breathe in more air per kilogram of body weight than an adult. They also spend more time closer to ground because of their height. Toluene vapors, being heavier than air, tend to concentrate closer to the ground, thereby increasing the risk of exposure for children. No data are available on the exposure of the children to toluene present in the air.

Means of protecting young children from ingestion of home products containing toluene need study and action. Child-proof containers and clearer warnings to parents should be considered to avoid unwanted exposure.

Child health data needs relating to susceptibility are discussed in Section 2.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for toluene were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.8.2 Ongoing Studies

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 toluene 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.

A number of ongoing research efforts will provide data regarding the potential for human exposure to toluene. These projects are summarized in Table 5-3. The EPA is also sponsoring the National Human Adipose Tissue Survey (NHATS), and this will provide additional data on the range of concentrations of toluene found in human fat samples taken during surgery or autopsy.

Table 5-3. Ongoing Studies on the Potential for Human Exposure to Toluene

Investigator	Affiliation	Research description	Sponsor
Christiani, D.C.	Harvard School of Public Health	Effects on reproductive outcome of occupational exposure to aromatic solvents in the oil industry	NIOSH
Alexander, M.	Cornell University	Effects of aging of pollutants for soil on bioavailability	NIEHS
Rappaport, S.M.	University of North Carolina, Chapel Hill	Development and application of biomarkers of exposure	NIEHS
Abroila, L.M.	Michigan State University	Persistence of NAPL contaminants in natural subsurface systems	NIEHS
Balster, R.L.	Texas Tech University	Behavioral pharmacology of abused solvents	NIDA
Spormann, A.M.	Stanford University	Enzymatic studies on the initial steps of anaerobic toluene and xylene metabolism	NSF

NIDA = National Institute of Drug Abuse; NIEHS = National Institutes of Health Science; NIOSH = National Institute for Occupational Safety and Health; NSF = Nation Science Foundation

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL SAMPLES

Toluene can be determined in biological fluids and tissues and breath using a variety of analytical methods. Representative methods are summarized in Table 6-1. Most analytical methods for biological fluids use headspace gas chromatographic (GC) techniques. Breath samples are usually collected on adsorbent traps or in sampling bags or canisters, and then analyzed by GC.

Because of its volatility, toluene is lost from biological samples, such as plant and animal tissue and body fluids, relatively easily. Therefore, samples must be collected and stored with care (e.g., at low temperatures in sealed containers) to prevent analyte loss. Blood samples are best stored at 4 EC or below, in full containers made from glass, Teflon, or aluminum components (Gill et al. 1988; Saker et al. 1991). Storage time must be limited to minimize losses. Contamination can occur during sampling or analysis since toluene is widely used as a solvent. Care must be taken to monitor for contamination.

Headspace techniques are usually used to separate toluene from biological fluids such as blood and urine. The headspace method involves equilibrium of volatile analytes such as toluene between a liquid and 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

Table 6-1. Analytical Methods for Determining Toluene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Lyse; extraction with carbon disulfide	GC/FID	No data	No data	Benignus et al. 1981
Blood	Purge and trap	No data	7.5 µg/L	No data	Cocheo et al. 1982
Whole blood	Purge and trap	GC/MS	0.088 µg/L	91–147	Ashley et al. 1992
Blood	Purge and trap	cap. GC/FID	50 ng/L	50	Fustinoni 1996
Blood	Headspace extraction	cap. GC/ITD	0.04 µmol/L	No data	Schuberth 1994
Mother's milk	Purge and trap	cap. GC/FID	No data	63 (chloro-benzene)	Michael et al. 1990a Pellizzari et al. 1982
Urine	Purge and trap	cap. GC/FID	50 ng/L	59	Fustinoni 1996
Urine	Heated headspace extraction	cap. GC/FID	1 ng/mL	42.3	Lee et al. 1998b
Biofluids	Headspace extraction	GC/FID	No data	No data	Suitheimer et al. 1982
Adipose tissue	Evaporation at 150 EC into nitrogen, direct gas injection	GC/FID	No data	88–112	Carlsson and Ljungquist 1982
Brain tissue	Extraction with carbon disulfide; homogenization; centrifugation	GC/FID	No data	No data	Benignus et al. 1981
Breath	Collection in modified Haldane-Priestly tube; transfer to adsorption tube; thermal desorption	cap. GC/MS	1 nmole	No data	Dyne et al. 1997
Breath	Collection via spirometer into passivated canisters	cap. GC/MS	low µg/m^3	80–136	Thomas et al. 1991
Breath	Collection via spirometer into 1.8 L passivated canisters	cap. GC/MS	~2 µg/m^3	91–104	Thomas et al. 1992
Breath	Collection via spirometer onto charcoal traps; microwave desorption	cap. GC/MS-SIM	3 µg/m^3	No data	Riedel et al. 1996

cap. = capillary; FID = flame ionization detector; GC = gas chromatography; ITD = ion trap detection; MS = mass spectrometry; SIM = selected ion monitoring

formation (Seto 1994). Packed columns and capillary columns are used for chromatographic separation, followed by identification and quantitation using various detectors; flame ionization detection (FID), photoionization detection (PID), 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.

A sensitive and reliable method for identification and quantitation of toluene in samples of whole blood taken from humans following exposure to volatile organic compounds (VOCs) has been developed by Ashley and coworkers at the Centers for Disease Control and Prevention (Ashley et al. 1992, 1996). 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 (91–147% recovery) and precision (12% RSD) for monitoring toluene in the population. Most modern purge and trap methods provide detection limits in the ppt range for toluene in both blood and urine (Ashley et al. 1992; Fustinoni et al. 1996).

Few methods are available for the determination of methylbenzene in other body fluids and tissues. Toluene may be extracted from biological materials using solvents such as carbon disulfide (Benignus et al. 1981); homogenization of tissue with the extractant and lysing of cells improves extraction efficiency. Care must be taken to avoid loss of low-boiling compounds. Highly purified solvents may be used to minimize problems with solvent impurities. A modified dynamic headspace method for 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). Supercritical fluid extraction using pure carbon dioxide or carbon dioxide with additives has good potential for the extraction of organic analytes such as toluene from biological samples.

Sensitive, reliable methods are available for measuring toluene in breath. Exhaled breath is collected in modified Haldane-Priestly tubes (Dyne et al. 1997), into passivated canisters (Thomas et al. 1992), or directly onto adsorbent traps (Riedel et al. 1996). The detection limits are in the low $\mu g/m^3$ range (Riedel et al. 1996; Thomas et al. 1991, 1992); accuracy, where reported, is good ($80%) (Riedel et al. 1996; Thomas et al. 1991, 1992).

Representative methods for determination of biomarkers of exposure to toluene are shown in Table 6-2. Measurement of toluene in blood (Kawai et al. 1993), urine (Kawai et al. 1996) and exhaled air (Lapare et al. 1993) provide reliable markers of exposure to toluene. Measurement of toluene metabolites is also utilized for monitoring toluene exposure in humans. Hippuric acid is formed in the body by the metabolism of toluene, and it is the glycine conjugate of benzoic acid. High performance liquid chromatography (HPLC) with ultraviolet (UV) detection is usually used for determination of hippuric acid in urine (Kawai et al. 1993; NIOSH 1984a). Other metabolites such as o-cresol (Kawai et al. 1996), benzylmercapturic acid (BMA) (Maestri et al. 1997), or S-p-toluylmercapturic acid (Angerer 1998a, 1998b) may also be measured. o-Cresol is a sensitive marker, but may arise from compounds other than toluene; the usefulness of BMA may be limited by variability among individuals.

6.2 ENVIRONMENTAL SAMPLES

Methods are available for determining toluene in a variety of environmental matrices. A summary of representative methods is shown in Table 6-3. Validated methods, approved by agencies and organizations such as EPA, ASTM, APHA, and NIOSH, are available for air, water, and solid waste matrices. GC is the most widely used analytical technique for quantifying concentrations of toluene in environmental matrices. Various detection devices used for GC include FID, MS, and photoionization detection (PID). Because of the complexity of the sample matrix and the usually low concentrations of VOCs in 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 methylbenzene 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. Purge-and-trap is the most widely used method for the isolation and concentration of VOCs in environmental samples (Lesage et al. 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.

Sampling techniques for air include collection in sample loops, on adsorbent, in canisters, and by cryogenic trapping. The analysis is normally performed by GC/FID, GC/PID, or GC/MS. Detection limits depend on the amount of air sampled, but values in the ppt range have been reported (Dewulf and Van Langenhover 1997).

Table 6-2. Analytical Methods for Determining Biomarkers of Toluene in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (Toluene)	Headspace	GC	No data	No data	Kawai et al. 1993
Urine (Toluene)	Headspace	GC/FID	2 µg/L	No data	Kawai et al. 1996
Urine (HA)	Extraction with ethyl acetate; evaporation; redissolve in water	HPLC/UV	30 mg/L	No data	NIOSH 1984b
Urine	Extraction with MTBE, elution with phosphate buffer/methanol/ formaldehyde	HPLC	0.1 mmol	101	Tardif et al. 1989
Urine (*o*-Cresol)	Hydrolysis; solvent extraction	HPLC/UV	0.5 mg/L	95[a]	Kawai et al. 1996
Urine (BMA)	Adsorbent column cleanup; derivatization	HPLC/FI	0.5 µg/L	No data	Maestri et al. 1997
Breath	Collection in Tedlar bags	GC/FID	No data	No data	Lapare et al. 1993

[a]Extraction efficiency

BMA = benzylmercapturic acid; FID = flame ionization detector; FI = fluorescence detector; GC = gas chromatography; HA = hippuric acid; HPLC = high performance liquid chromatography; MTBE = methyl tertiary butyl ether; UV = ultraviolet detection

Table 6-3. Analytical Methods for Determining Toluene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Workplace air	Sorption on activated carbon; extraction with carbon disulfide	GC/FID	0.01 mg	±11.4[a]	NIOSH 1994 Method 1501
Air	Sorption onto Tenax®; solvent extraction; thermal desorption	GC/MS	<0.88 ppb	111–163	Crist and Mitchell 1986
Air	Sorption onto Tenax®; thermal desorption	GC/MS	No data	93–94	EPA 1988a Method TO-1 Krost et al. 1982
Air	Collection in passivated canisters	GC/MS	low ppb	No data	EPA 1988b Method TO-14
Air	Collection on multisorbent tubes; thermal desorption	GC/MS	No data	No data	EPA 1997a Method TO-17
Air	Collection in sorbent sampler tubes	GC/FID	0.01 mg/sample	94	USEPA, EMMI 1997 NIOSH 1500
Air	Sorption on activated charcoal; extraction with carbon disulfide	GC/FID	0.01 mg/sample	No data	USEPA, EMMI 1997 NIOSH 4000
Stack gas effluents	Sorption onto Tenax®; thermal desorption	GC/MS	No data	50–150	USEPA, EMMI 1997 OSW 5041A
Vehicle exhaust	Direct	GC/FID	0.5 ppb	No data	Dearth et al. 1992
Drinking water	Purge and trap	cap. GC/PID	0.01–0.02 ppb	98–99	EPA 1991a Method 502.2
Drinking water	Purge and trap	GC/PID	0.02 ppb	94	EPA 1991b Method 503.1
Drinking water	Purge and trap	cap. GC/MS	0.08–0.11 ppb	100–126	EPA 1992a Method 524.2

Table 6-3. Analytical Methods for Determining Toluene in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water/ waste water	Purge and trap	GC/PID	0.2 ppb	77	EPA 1982b Method 602
Water/ waste water	Purge and trap	GC/MS	6.0 ppb	98–101	EPA 1982c Method 624
Water/ waste water	Addition of isotopically labeled analog; purge and trap	GC/MS	10 ppb	No data	EPA 1984 Method 1624
Industrial effluents	Purged with inert gas onto Tenax®; thermally desorbed	GC/IDMS	20 ppb	No data	Colby et al. 1980
Drinking water, waste water	Purged with inert gas onto Tenax®; thermally desorbed, cryofocused	GC/MS	1 ppb	74–107	Michael et al. 1988
Groundwater	Solid-phase microextraction	GC/FID	2 ppb	No data	Arthur et al. 1992
Water	Purge and trap	GC/MS	0.047 ppb	106	USEPA, EMMI 1997 APHA 6210-B
Water	Direct aqueous injection	GC	1.0 ppm	No data	USEPA, EMMI 1997 ASTM D3695
Water	Purge and trap	GC	0.5 ppb	80–120	USEPA, EMMI 1997 APHA 6220-B
Water	Dilution in appropriate solvent	FS	2.1 ppm	No data	USEPA, EMMI 1997 ASTM D4763
Groundwater, aqueous sludges, waste solvents, acid and caustic liquors, soils, sediments	Purge and trap	GC/MS	5 ppb	47–150	USEPA, EMMI 1997 OSW8240B-W

Table 6-3. Analytical Methods for Determining Toluene in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, aqueous sludges, waste solvents, acid and caustic liquors, soils, sediments	Purge and trap or direct injection	GC/EC or GC/PID	0.01 ppb	99	USEPA, EMMI 1997 OSW 8021B-PID
Solid waste	Purge-and-trap	cap. GC/PID	0.01 ppb	99	EPA 1996a Method 8021B
Solid waste	Purge-and-trap	GC/PID	0.08–0.11 ppb	100–102	EPA 1996b Method 8260B
Soil	Methanol extraction; SPE	cap. GC	sub-ppm	>90	Meney et al. 1998
Soil (screening)	Filter	immunoassay	7 ppm	No data	EPA 1996c Method 4030
Soils and sediments	Headspace extraction	GC/PID	0.2 ppb	46–148	USEPA, EMMI 1997 OSW 8020A
Soids and other solid matrices	Headspace extraction	GC/FID GC/PID/ELCD	No data	No data	USEPA, EMMI 1997 OSW 5021
Solid waste matrices	Purge and trap or direct aqueous injection or concentration by azeotropic distillation or automated static headspace	GC/MS	0.11 ppb	102	USEPA, EMMI 1997 OSW 8260B
Plant cuticle	Headspace extraction	GC/FID	No data	No data	Keymeulen et al. 1997
Food	Headspace extraction, 1 hour at 90 EC	GC	No data	No data	Walters 1986

Table 6-3. Analytical Methods for Determining Toluene in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Foods	Purge and trap	cap. GC/MS	8 ppb	54–76[b]	Heikes et al. 1995
Bottled water	Headspace extraction	GC/MS	0.5-1 ppb	No data	Page et al. 1993
Olive oil	Homogenization; headspace	cap. GC/MS	No data	No data	Biedermann et al. 1995

[a]Reported accuracy
[b]Intralaboratory accuracy. Single lab accuracy is reported as 100–106% recovery.

cap. = capillary; FID = flame ionization detector; FS = fluorescence spectroscopy, ELCD; GC = gas chromatography; IDMS = isotope dilution mass spectrometry; MS = mass spectrometry; PID = photoionization detector; SPE = solid-phase extraction

Toluene may be determined in occupational air using collection on adsorbent tubes, solvent desorption and GC/FID analysis (NIOSH 1994). Detection limits depend upon the amount of air sampled; accuracy is very good (11.4% bias) (NIOSH 1994). Passive samplers are also used (Ballesta et al. 1992; Periago et al. 1997); however, little performance data are available.

Gas purge and trap is the most widely used method for the isolation and concentration of VOCs in environmental samples (Lesage et al. 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 less than 1 µg of methylbenzene per liter of sample have been achieved. Very low detection limits for drinking water are reported for the purge and trap method with GC/PID (0.01–0.02 ppb) (EPA 1991a, 1991b). Accuracy is very good (94–99% recovery) (EPA 1991a, 1991b). While the analytical method is selective, confirmation using a second column or GC/MS is recommended (EPA 1992a). Good sensitivity (0.08–0.11 ppb) and accuracy (100–126% recovery) can also be obtained using capillary GC/MS detection (EPA 1992a). Purge-and-trap methodology may be applied to waste water as well (EPA 1982b, 1982c, 1984). Sensitivity is in the low ppb range and recovery is good (77–101%) (EPA 1982b, 1982c, 1984).

Soil, sediment, and solid waste are more difficult to analyze. Volatilization during sample handling and homogenization can result in analyte loss. Purge-and-trap methods with capillary GC/PID or GC/MS analysis provide detection limits of approximately 0.5 ppm for wastes and 5 µg/g for soil and sediment (EPA 1982b, 1982c, 1984).

No methods were found for the determination of toluene in fish and biota. Few methods are available for the determination of toluene in food. A purge and trap extraction method is available for determining toluene in a variety of foods. The quantitation limit is 8 ppb; single lab recovery is very good (100–106%) and precision is good (9.8–25% RSD). Both intra- and inter-laboratory studies were conducted, and precision was found to be #25% RSD (Heikes et al. 1995).

6.3 ADEQUACY OF THE DATABASE

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

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Although toluene and its metabolites can be measured in body fluids using a number of techniques (Kawai et al. 1993, 1996; NIOSH 1984a,), the metabolites have limited value as biomarkers. A number of common food materials produce the same metabolites, thus measurement of toluene metabolites can be used to confirm a known exposure but cannot be used to determine whether or not exposure occurred in a poorly defined situation. It is also very difficult to quantify the magnitude of exposure from levels of either toluene or its metabolites in biological samples. Despite these limitations, end-of-shift concentrations of 2.5 g hippuric acid/g creatinine and 1.0 mg/L toluene *in venous* blood have been established as biological exposure indices for toluene (ACGIH 1992a). A technique that could accurately quantify exposure to toluene would be useful.

For occupational health monitoring and animal studies, there is also a need for improved and more sensitive methods to determine toluene metabolites. Additional work to develop sensitive methods for analysis of the cresol metabolites and to correlate these metabolites with specific exposure conditions would be valuable.

It is equally difficult to monitor the effects of toluene exposure. Magnetic resonance imaging (MRI) and BAER evaluations of the brain have some value in determining the neurological damage resulting from long-term exposures to high levels of toluene, but have no known value for determining the effects of low-level and/or short-term exposures.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. There are methods available for the determination of toluene and its metabolites in environmental samples. Sensitive techniques for air allow detection of toluene at levels as low as 0.88 ppb (Crist and Mitchell 1986). In drinking water, detection limits of 0.01–0.02 µg/L are possible using GC/MS or GC/PID (EPA 1991a, 1991b). For waste water, detection limits in the low ppb range are achievable (EPA 1982b, 1982c, 1984). These techniques are adequate to measure both background toluene levels and the levels of toluene in environmental media that could cause health effects. However, when toluene is present in combination with other volatile materials, interference from the companion volatiles often raises the detection limit and decreases the accuracy and precision of the technique. Improved methods for separation of toluene from other volatiles would be useful.

Very little work has been conducted on measuring the levels of toluene metabolites in the environment. Although techniques for measuring these substances exist, they have not routinely been applied to environmental media. Research on measuring the levels of metabolites in soil and water would be valuable especially in studying the end products of microbial degradation. Few methods are available for monitoring toluene in foods; reliable methods are needed for evaluating the potential for human exposure that might result from toluene ingestion.

6.3.2 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 toluene and other volatile organic compounds in blood. These methods use purge-and-trap methodology, high-resolution GC, and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion (ppt) range.

The U.S. EPA is conducting a pilot program for comprehensive monitoring of human exposure. The National Human Exposure Assessment Study (NHEXAS) is being conducted in three regions of the United States in order to establish relationships between environmental concentrations, exposure, dose, and health response and to determine the incidence and causes of high exposures, especially for biologically susceptible persons. One of the aims of the pilot study is to test measurement methodology for a variety of pollutants, including toluene, in air and water. As an adjunct to this pilot study, the U.S. EPA and the State of Minnesota are conducting a study of children's exposure to toxic chemicals, including toluene.

7. REGULATIONS AND ADVISORIES

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

ATSDR has derived an acute-duration inhalation MRL of 1 ppm (3.8 mg/m^3) for toluene based on a NOAEL for neurological effects in humans (Andersen et al. 1983).

ATSDR has derived a chronic-duration inhalation MRL of 0.08 ppm (0.3 mg/m^3) for toluene based on a LOAEL for neurological effects in humans in a study by Zavalic et al. (1998a).

ATSDR has derived an acute-duration oral MRL of 0.8 mg/kg/day for toluene based on a LOAEL for neurological effects in rats (Dyer et al. 1988).

ATSDR has derived an intermediate-duration oral MRL of 0.02 mg/kg/day for toluene based on a LOAEL for neurological effects in mice (Hsieh et al. 1990b).

The EPA's reference concentration (RfC) for toluene is 0.4 mg/m^3 and the EPA's reference dose (RfD) is 0.2 mg/kg/day (IRIS 2000).

The International Agency for Research on Cancer (IARC) classifies toluene as a Group 3 carcinogen (the agent is not classifiable as to its carcinogenicity to humans) based on inadequate evidence in humans for carcinogenicity of toluene and evidence suggesting lack of carcinogenicity of toluene in experimental animals (IARC 1999). The EPA and the American Conference of Governmental Industrial Hygienists (ACGIH) also state that there are inadequate data on which to classify toluene in terms of its carcinogenicity in humans or animals (ACGIH 1997; IRIS 2000). Therefore, toluene is assigned the cancer classification of “Group D” by the EPA and given the cancer category “A4" by the ACGIH (ACGIH 1997; IRIS 2000).

Toluene is listed as a chemical which must meet the requirements of Section 313 of Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1996a). Title III of SARA, also known as "The Emergency Planning and Community Right-to-Know Act of 1986," requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually any release of those chemicals to any environmental media over a specified threshold level.

Toluene has been designated as a hazardous substance pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 1995a). The statutory source for this designation is Section 311(b)(4) of the Clean Water Act (CWA), Section 307 (a) of the CWA, Section 112 of the Clean Air Act (CAA), and Section 300 of the Resource Conservation and Recovery Act (RCRA) (EPA 1995a). The owner and operator of any facility that produces, uses, or stores a CERCLA hazardous substance is required to immediately report releases to any environmental media, if the amount released is equal to or exceeds the specified "reportable quantity" assigned to the substance. The reportable quantity for toluene is 1,000 pounds (454 kg) (EPA 1995a).

The Occupational Safety and Health Administration (OSHA) sets permissible exposure limits (PELs) to protect workers against adverse health effects resulting from exposure to hazardous substances. The PELs determined for hazardous substances are enforceable, regulatory limits on allowable air concentrations in the workplace. OSHA requires employers of workers who are occupationally exposed to these hazardous substances to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). Between June 27, 1974 and January 18, 1989, the Occupational Safety and Health Administration (OSHA) had promulgated protective, permissible exposure limits (PELs) for approximately 264 toxic substances (OSHA 1993). On January 18, 1989, OSHA promulgated more protective PELs for approximately 376 toxic substances. Toluene was included among the 212 toxic substances for which the PEL was lowered (OSHA 1989a). The new PELs for toluene were set at 50 ppm (TWA) and 100 ppm for the 15-minute, short-term exposure limit (STEL) (OSHA 1989a). Because the 1989 promulgation was rescinded by the 11th Circuit Court Appeals in July 1992, only those PELs in place prior to the 1989 rule are currently enforced by OSHA. On June 30, 1993, OSHA published in the Federal Register a final rule announcing the revocation of the 1989 exposure limits, including the newly established limits for toluene (OSHA 1993). An employer must ensure that an employee's exposure to toluene in any 8-hour work shift of a 40-hour week does not exceed the 8-hour time-weighted average (TWA) of 200 ppm (OSHA 1974). The acceptable ceiling concentration for toluene which shall not be exceeded at any time during an 8-hour shift is 300 ppm (OSHA 1974). The acceptable maximum peak above the ceiling for an 8-hour shift is 500 ppm. The maximum exposure duration for this level is 5 minutes in any 2-hour period (OSHA 1974). The ACGIH (1999) recommends an 8-hour TWA Threshold Limit Value of 50 ppm toluene to protect against central nervous system effects.

Toluene is regulated as a hazardous air pollutant (U.S. Congress 1990) and is subject to the emission limitations for various processes and operations in the synthetic organic chemicals manufacturing

industry (EPA 1983a, 1993b, 1995i). Source categories such as wood furniture manufacturing operations (EPA 1995g), polymer and resin producers (EPA 1996c) and petroleum refineries (EPA 1996b) that could release toluene to the atmosphere must meet the national emissions standards for hazardous air pollutants (NESHAPs).

Because of its potential to cause adverse health effects in exposed people, toluene is also regulated by the drinking water standards set by the EPA. Toluene generally gets into drinking water by improper waste disposal or leaking underground storage tanks. In order to protect humans from the risk of developing adverse health effects from exposure to toluene through drinking water, the EPA Drinking Water Regulations and Health Advisories (1996) lists the Maximum Contaminant Level and the Maximum Contaminant Level Goal for toluene as 1 mg/L.

Table 7-1. Regulations and Guidelines Applicable to Toluene

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Cancer Classification	Group 3	IARC 1998
WHO	Drinking-water guideline values for health-related organics	700 µg/L	WHO 1996
NATIONAL Regulations and Guidelines:			
a. Air:			
ACGIH	TLV—TWA	50 ppm	ACGIH 1999
EPA	Listed as a Hazardous Air Pollutant	Yes	Clean Air Act Amendment, Title III, Section 112 (b) U.S. Congress 1990
NIOSH	Recommended Exposure Limit: TWA STEL	 100 ppm 150 ppm	NIOSH 1999
OSHA	8-hour time weighted average	200 ppm	29 CFR 1910.1000 OSHA 1999a
	Acceptable ceiling concentration	300 ppm	29 CFR 1910.1000 OSHA 1999a
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift for a maximum duration of 10 minutes	500 ppm	29 CFR 1910.1000 OSHA 1999a
	Vacated 1989 OSHA PEL[a] TWA STEL	 100 ppm 150 ppm	OSHA 1989a
	8-hour time weighted average for shipyard workers	200 ppm	29 CFR 1915.1000 OSHA 1999b
	8-hour-time weighted average for construction workers	200 ppm	29 CFR 1926.55 OSHA 1999c
b. Water			

Table 7-1. Regulations and Guidelines Applicable to Toluene *(continued)*

Agency	Description	Information	Reference
EPA (cont.)	MCLG	1 mg/L	40 CFR 141.50 EPA 1999g
EPA	MCL	1 ppm	40 CFR 141.32 EPA 1999f
	MCL for community and non-transient, non-community water systems	1 mg/L	40 CFR 141.61 EPA 1999h
	Health Advisories One-day (10-kg child) Ten-day (10-kg child) Longer-term (child) Longer-term (adult) Lifetime (adult) Cancer Classification	 20 mg/L 2 mg/L 2 mg/L 7 mg/L 1 mg/L Group D[b]	EPA 1996a
	Water Quality Criteria: water and organisms organisms only	 6,800 µg/L 200,000 µg/L	EPA 1999j
	Universal treatment standards waste water non-waste water	 0.080 mg/L[2] 10 mg/kg[3]	40 CFR 268.48 EPA 1999e
FDA	Bottled water limit for toluene	1 mg/L	21 CFR 165.110 FDA 1999e
c. Food			
EPA	Residue exempt from the requirement of a tolerance when used in accordance with good agricultural practice in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest	Used as a solvent or co-solvent	40 CFR 180.1001 EPA 1999i
FDA	Indirect Food Additive—component of adhesives	Yes	21 CFR 175.105 FDA 1999a
	Indirect food additive—component of resinous and polymeric coatings	Yes	21 CFR 175.320 FDA 1999c
	Indirect food additive— residual solvent in finished polycarbonate resins	Not to exceed 800 ppm	21 CFR 177.1580 FDA 1999d

Table 7-1. Regulations and Guidelines Applicable to Toluene *(continued)*

Agency	Description	Information	Reference
FDA (cont.)	Used as an adjuvant in the manufacturing of foam plastics intended for use in contact with foods— subject to the following limitations:	Use only as a blowing agent adjuvant to polystyrene at a level not to exceed 0.35% by weight of finished foam polystyrene	21 CFR 178.3010 FDA 1999b
	Indirect food additive— component of cellophane used for food packaging	Residue limit of 0.1%	21 CFR 177.1200 FDA 1999f
d. other			
ACGIH	Cancer classification	A4[c]	ACGIH 1999
	Biological Exposure Index: *o*-Cresol in urine Hippuric acid in urine Toluene in blood	 0.5 mg/L 1.6 g/g creatinine 0.05 mg/L	
EPA	RfD RfC Cancer Classification	0.2 mg/kg/day 0.4 mg/m^3 D[d]	IRIS 2000
	Reportable quantity for toluene regarded as a CERCLA hazardous substance under section 311(b)(4), 307(a) and 112 of the Clean Water Act; and by RCRA section 3001	1,000 lb	40 CFR 302.4 EPA 1999b
	Identification and Listing of toluene as a Hazardous Waste	Yes	40 CFR 261.33 EPA 1999a
	Toxic pollutant designated pursuant to section 307(a)(1) of the Act	Yes	40 CFR 401.15 EPA 1998a
	Toxic Chemical Release Reporting— effective date	1/1/87	40 CFR 372.65 EPA 1999d
EPA (cont.)	Designated hazardous substance in accordance with section 311(b)(2)(a) of the Act	Yes	40 CFR 116.4 EPA 1998b
	Health and Safety Data Reporting Rule	Yes	40 CFR 716.120 EPA 1995f

Table 7-1. Regulations and Guidelines Applicable to Toluene *(continued)*

Agency	Description	Information	Reference
STATE			
a. Air:			
Arizona	Acceptable concentration		NATICH 1992
	1-hour	1 ppm	
	24-hour	0.796 ppm	
Connecticut	8-hour acceptable concentration	7,500 µg/m^3	NATICH 1992
Florida	Acceptable concentration		NATICH 1992
	Fort Lauderdale		
	8-hour	7.5 mg/m^3	
	Pinella		
	8-hour	3,750 µg/m^3	
	24-hour	900 µg/m^3	
	Annual	300 µg/m^3	
Idaho	Acceptable concentration	18.75 mg/m^3	ID Dept Health Welfare 1999a
	Occupational exposure level	375 mg/m^3	
Indiana	8-hour acceptable concentration	1,880 µg/m^3	NATICH 1992
Kansas	Concentration limits for hazardous air emissions	10 tons/year	KS Dept. Health Env 1998b
Louisiana	8-hour acceptable concentration	8,900 µg/m^3	NATICH 1992
Massachusetts	24-hour and annual acceptable concentration	10.20 µg/m^3	NATICH 1992
Maine	Acceptable concentration		NATICH 1992
	24-hour	260 µg/m^3	
	Annual	180 µg/m^3	
North Carolina	Acceptable concentration		NATICH 1992
	15-minute	56 mg/m^3	
	24-hour	4.7 mg/m^3	
North Dakota	Acceptable concentration		NATICH 1992
	8-hour	3.77 mg/m^3	
	1-hour	5.65 mg/m^3	
Nevada	8-hour acceptable concentration	8.93 mg/m^3	NATICH 1992
New York	Annual Acceptable concentration	7,500 µg/m^3	NATICH 1992
Oklahoma	24-hour acceptable concentration	37,500 µg/m^3	NATICH 1992

Table 7-1. Regulations and Guidelines Applicable to Toluene *(continued)*

Agency	Description	Information	Reference
STATE (cont.)			
Rhode Island	Acceptable concentration 24-hour Annual	 2,000 µg/m^3 400 µg/m^3	RI Dept Env Management 1992
South Dakota	8-hour acceptable concentration	7,500 µg/m^3	NATICH 1992
Texas	0.5-hour acceptable concentration	3,750 µg/m^3	NATICH 1992
Virginia	24-hour acceptable concentration	6,300 µg/m^3	NATICH 1992
Vermont	24-hour acceptable concentration	8,930 µg/m^3	NATICH 1992
Washington	24-hour acceptable concentration	1,250 µg/m^3	NATICH 1992
Wisconsin	Acceptable emission levels <25 feet 25 feet	 31 lbs/hour 131 lbs/hour	WI Dept Natural Resources 1997
EPA Region 9[e]	Preliminary remedial goal (non cancer)	4.0 x 10^{+2} µg/m^3	EPA 1998a
b. Water			
Alabama	Human health criteria for consumption of: water and fish[f] fish only[f]	 6 mg/L 43.6 mg/L	AL Dept Env Management 1998
Alaska	Maximum contaminant level	1 mg/L	AK Dept Env Conserv 1999
Arizona	Human health based guidance levels (HBGLS)for ingestion of contaminents in drinking water Oral HBGL MCL	 1400 µg/L 1000 µg/L	AR Dept Health Services 1999
	Aquifer water quality standard-drinking water protected use	1 mg/L	BNA 1998
California	Drinking water guideline	100 µg/L	FSTRAC 1995

Table 7-1. Regulations and Guidelines Applicable to Toluene *(continued)*

Agency	Description	Information	Reference
STATE (cont.)			
Colorado	Aquatic life based criteria for surface waters:		CO Dept Public Health Env 1999
	acute	17,500 µg/L	
	chronic	Not given	
	Human health based for surface water:		
	water and organism	1000 µg/L	
	water only	1000 µg/L	
Connecticut	Drinking water guideline	1,000 µg/L	FSTRAC 1995
	Surface-water protection criteria for substances in ground water	$4x10^{+6}$ µg/L	BNA 1998
Delaware	Freshwater fish ingestion	370 mg/L	BNA 1998
	Freshwater fish and water	10 mg/L	
	Marine fish ingestion	52 mg/L	
Florida	Criteria for resource protection and recovery		BNA 1998
	freshwater	475 µg/L	
	marine	475 µg/L	
Hawaii	Health guidelines applicable to all water:		HI Dept Health 1999a
	Freshwater		
	acute	5,800 µg/L	
	chronic	NS[g]	
	Saltwater		
	acute	2,100 µg/L	
	chronic	NS[g]	
	Fish consumption	140,000 µg/L	
	MCL applicable to community and non-transient, non-community water systems	1 mg/L	HI Dept Health 1999b
Idaho	Ground water quality	1 mg/L	ID Dept Health Welfare 1999a
Illinois	Human health standards	51.0 mg/L	IL Env Protec Agency 1999
Kansas	Guideline	2,000 µg/L	FSTRAC 1990
Kansas	Surface water quality standards for aquatic life:		KS Dept Health Envment 1998a
	acute	17,500 mg/L	
	chronic	Not given	
Maine	Guideline	1400	FSTRAC 1995

Table 7-1. Regulations and Guidelines Applicable to Toluene *(continued)*

Agency	Description	Information	Reference
STATE (cont.)			
Massachusetts	Guideline	2,000 µg/L	FSTRAC 1995
Minnesota	Guideline	1,000 µg/L	FSTRAC 1995
New Hampshire	Guideline	2,000 µg/L	FSTRAC 1990
New Jersey	Ground water quality standards	1000 µg/L	NJ Dept Env Protec 1993
Oklahoma	Aquatic life Criteria acute chronic	 Not given 875.0 µg/L	OK Dept Env Quality 1997
Rhode Island	Accepted level - annual average	2,000 µg/m^3	RI Dept Env Management 1992
South Dakota	Maximum contaminant levels—apply to community and non-transient and non-community water systems	1 mg/L	SD Dept Env Natural Resources 1998
Vermont	Guideline	2,420 µg/L	FSTRAC 1995
Wisconsin	Standard	1,000 µg/L	FSTRAC 1995
EPA Region 9[e]	Preliminary remedial goal (noncancer)	$7.2x10^{+2}$ µg/m^3	EPA 1998a

[a]OSHA set more protective PELs for 212 substances in 1989. However, in July 1992, the 11th Circuit Court Appeals rescinded the 1989 PELs promulgated by OSHA. Only PELs in place prior to the 1989 rule are currently allowed as OSHA standards.
[b]Not classifiable; Inadequate or no human and animal evidence of carcinogenicity
[c]A4-Not classifiable as a human carcinogen.
[d]D-substances are unclassifiable as to their carcinogenicity
[e]The preliminary remediation goals (PRGs) are tools used by EPA Region 9 for evaluating and cleaning up contaminated sites. They are being used to streamline and standardize all stages of the risk decision-making process for soil remediation.

[f]The following equations were used to calculate the values as given in the Alabama State laws:
Consumption of water and fish: Concentration (mg/L) = (HBW X RfD) / [(FCR X BCF) + WCR]
Consumption of water only:
Concentration (mg/L) = (HBW X RfD) / (FCR X BCF)
HBW = human body weight, set at 70 kg
RfD = reference dose, 0.2 mg/(kg-day) for toluene
FCR = fish consumption rate, set at 0.030 kg/day
BCF = bioconcentration factor, 10.7 L/kg for toluene
WCR = water consumption rate, set at 2 L/day

[g]NS: no standard has been developed

ACGIH=American Conference of Governmental Industrial Hygienists; CFR=code of federal regulations; CPSC=Consumer Product Safety Commission; EPA=Environmental Protection Agency; FDA=Food and Drug Administration; FR=federal register; FSTRAC=Federal-State Toxicology and Regulatory Alliance Committee; IARC=International Agency for Research on Cancer; IRIS=Integrated Risk Information System; MCL=maximum contaminant level; MCLG=maximum contaminant level goal; NIOSH=National Institute for Occupational Safety and Health; NPDES=national pollutant discharge elimination system; OSHA=Occupational Safety and Health Administration; PEL=permissible exposure limit; RfC=inhalation reference concentration; RfD=oral reference dose; STEL=short term exposure limit; TLV=threshold limit value; TWA=time-weighted average; WHO=World Health Organization

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9. GLOSSARY

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

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

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

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

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

Benchmark Dose (BMD)—is 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—is 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—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.

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 which 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 which 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.

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.

Immunological Effects—are functional changes in the immune response.

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

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

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

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which 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 which has been calculated to cause death in 50% of a defined experimental animal population.

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

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest 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—a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which 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 odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

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—is the science of quantitatively predicting 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—is 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 whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—is a type of physiologically-based dose-response model which 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—is 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 4such 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) concentrations 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 casual 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.

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 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

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 study of 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 one can be used; however a reduced UF of three may be used on a case-by-case basis, three 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.

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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 a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET(S)

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 17
Species: human

MRL: 1 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Andersen I, Lundqvist GR, Molhave L et al. 1983. Human response to controlled levels of toluene in six-hour exposures. Scand J Work Environ Health 9: 405-418.

Experimental design: The effects of toluene on 16 healthy young male subjects with no previous regular exposure to organic solvents were investigated. Groups of four subjects were in a chamber for 6 hours a day on 4 consecutive days. After 1 hour of exposure to clean air in the chamber, the concentration of toluene was steadily increased during 30 minutes to the concentration intended for the day. After hour of exposure, all subjects went through all physiological, discomfort, and performance measurements for the next 1.5 hours. After a 1 hour lunch, a similar series of measurements were made during the 5^{th} and 6^{th} hours of exposure. The concentration of toluene was 0, 10, 40, or 100 ppm with each group exposed to a different toluene concentration each day. Physiological measurements were performed, including nasal mucociliary flow, FVC, FEV, and FEF_{25-75}, and subjective measurements of discomfort. Eight different performance assessment tests (five-choice serial reaction test, rotary pursuit test, screw-plate test, Landolt's ring test, Bourdon Wiersma test, multiplication test, sentence comprehension test, and word memory test) were carried out.

Effects noted in study and corresponding doses: There was a significant change in nasal mucus flow from control values during all of the toluene exposures. During the 100 ppm exposure, statistically significant increased irritation was experienced in the eyes and in the nose, but not in the throat or lower airways. There was also a statistically significant increase in the occurrence of headaches, dizziness, and feelings of intoxication during the 100 ppm exposure, but not during the other concentrations. No statistically significant effects of toluene occurred in the eight performance tests. For three of the tests, multiplication test, Landolt's rings, and the screw plate test, there was a borderline correlation between toluene and the test results. The subjects felt that the tests were more difficult and strenuous during the 100 ppm exposure, for which headache, dizziness, and feelings of intoxication were more often reported. No adverse effects were reported at the 10 and 40 ppm levels.

Dose endpoint used for MRL derivation: 40 ppm for neurological effects

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

MRL = 40 ppm x 5 days/7 days x 8 hours/24 hours ÷10 = 1 ppm (3.8 mg/m^3)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

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

Was a conversion used from intermittent to continuous exposure? Exposure concentration was adjusted to continuous exposure basis as shown above.

Other additional studies or pertinent information that lend support to this MRL: The primary effect of toluene is on the central nervous system. There are several other human studies for which the central nervous system is the major end point and could have been used to derive an acute inhalation MRL. However, the Andersen et al. (1983) study was chosen as the basis for the MRL because this was the only human study which reported a NOAEL. Baelum et al.(1985) also reported a LOAEL of 100 ppm for neurological effects in humans. In this study, 43 occupationally-exposed subjects and 43 controls were exposed to either clean air or air containing 100 ppm toluene for 6.5 hours in a climate chamber. A battery of ten tests of visuomotor coordination, visual performance, and cortical function were administered during the 6.5 hour period. For both the controls and toluene exposed subjects, there were complaints of air quality, irritation of the nasal passages, and increased feelings of fatigue and sleepiness. Subjects also complained of headaches and dizziness. Toluene exposure decreased performance on four of the neurobehavioral tests; three of these were tests of visual perseverance. The fourth test affected was the simple peg board test of visuomotor function, where the effect was noted in toluene-exposed workers to a much greater extent than controls. Escheverria et al. (1991) reported a LOAEL of 75 ppm for neurological effects in humans. In this study, two groups of 42 students were exposed to 0, 75, and 150 ppm toluene for a 7 hour period. A complete battery of 12 tests was administered before and at the end of each exposure. Toluene caused a dose-related impairment of function on digit span pattern recognition, the one hole test, and pattern memory. Rahill et al. (1996) reported a LOAEL of 100 ppm for neurological effects in humans. In this study, six volunteers were exposed for 6 hours a day to either 100 ppm toluene or clean air. Three repetitions of two computerized neuropsychological tests were performed, with the composite score on the multitasking test being significantly lower with toluene exposure than with clean air.

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ]Intermediate [X] Chronic
Key to figure: 160
Species: human

MRL: 0.08 [ ] mg/kg/day [X] ppm [ ] mg/m^3

References: Zavalic, M, Mandic, Z, Turk, R et al. 1998a. Quantitative assessment of color vision impairment in workers exposed to toluene. Am J Ind Med 32: 297-304.

Zavalic, M, Mandic, Z, Turk, R et al. 1988c. Assessment of colour vision impairment in male workeres exposed to toluene generally above occupational exposure limits. Occup Med 48(3):175-180

Experimental design: Three groups of Croatian workers were examined by means of interviews, medical examination, and color vision testing using the Lanthony 15 Hue desaturated panel in standard conditions. Workers were excluded from the study if they met any of the following criteria: less than 6 months employment, congenital color vision loss, a medical condition which can affect color vision, visual acuity below 6/10, use of medications which can affect color vision or a hobby that involved solvent exposure. Alcohol intake and smoking were also assessed for each individual. The first group consisted of 46 workers (43 women and 3 men) employed in manually glueing shoe soles and exposed to median levels of 32 ppm and geometric mean levels of 35 ppm toluene. The second group consisted of 37 workers (34 men and 3 women) employed in a rotogravure printing press and exposed to median levels of 132 ppm and geometric mean levels of 156 ppm toluene. The third group consisted of 90 workers (61 men and 29 women) not occupationally exposed to any solvents or known neurotoxic agents. The average age of the workers was 41 years. The technology, ventilation and types of workplaces included in the study had not changed in the preceding 30 years. Toluene exposure was evaluated by mid-week environmental and biological monitoring of toluene. Samples of air were collected at 11 stations in the shoe factory and 8 locations in the printing press. Toluene levels were measured in blood samples taken at the beginning of the work shift (all workers). Orthocresol and hippuric acid levels in urine were measured (for printers only) at the end of the work shift.

Effects noted in study and corresponding doses: Comparison of mean values between groups was assessed by t-test or Mann-Whitney U-test. Correlations between variables were determined using linear multiple regression analyses. Analyses were performed using CCI or AACCI as dependent factors and age, alcohol intake, exposure duration, work service, toluene in air, toluene in blood, and biological markers of toluene in urine (printers only) as independent factors. A p-value <0.05 was regarded as significant. The mean CCI was significantly higher in printers compared to both shoemakers and controls. The Mean CCI for shoemakers was increased compared with controls, but the difference was not significant. Regression analysis of the control data indicated that alcohol intake and age were significant explanatory variables for changes in CCI. The age- and alcohol-adjusted color confusion index was significantly increased in printers (156 ppm) compared with both shoemakers (35 ppm) and controls, and in shoemakers (35 ppm) compared with controls. Regression analyses of the data from printers showed significant correlations between CCI as a dependent variable and age, alcohol intake, toluene in air, toluene in blood, hippuric acid in urine, or orthocresol in urine as independent variables.

Significant correlation was also found for AACCI as dependent variable and exposure to toluene or biomarkers of toluene exposure. In contrast, the shoemaker data showed a significant correlation between CCI and age, but did not establish any significant correlation between CCI or AACCI and any marker of toluene exposure. This study demonstrated a statistically significant impairment of color vision in workers chronically exposed to 156 ppm toluene compared with controls. When the data were adjusted to allow for the confounding effects of alcohol consumption and age, a significant difference due to toluene exposure was also reported for workers exposed to 35 ppm toluene compared with controls.

Dose endpoint used for MRL derivation: 35 ppm for alcohol-and age-adjusted color vision impairment

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [x] 10 (for use of a minimal LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

MRL = 35 ppm x 5 days/7 days x 8 hours/24 hours ÷ 100 = 0.08 ppm (0.3 mg/m^3)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

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

Was a conversion used from intermittent to continuous exposure? Exposure concentration was adjusted to continuous expsoure basis as shown above.

Other additional studies or pertinent information that lend support to this MRL: There are several other reports of subtle neurological impairments in toluene-exposed workers that support this MRL. Another group of printers exposed to mean concentrations of 120 ppm toluene had a significantly increased mean alcohol-and age-adjusted color confusion index compared with unexposed controls (Zavalic et al. 1998b). A group of printing press workers (exposed to average toluene concentrations of 50 ppm for an average of 30 years) had significantly reduced wave amplitude of visual evoked potentials and increased latency of auditory evoked potentials (Vrca et al. 1995, 1996, 1997a, 1997b). Significant changes in auditory evoked potentials were also reported for printers exposed to 97 ppm toluene for 12–14 years (Abbate et al. 1993). A study of hearing loss in Brazilian printers exposed to multiple solvents (toluene concentrations in air were reported as 0.14–919 mg/m^3 or 0.04–245 ppm) found that the odds ratio for hearing loss increased 1.76 times with each gram of hippuric acid/gram creatinine (Morata et al. 1997). Ten rotogravure printers (average exposure of 83 ppm for 1–36 years) examined for neurological effects were found to have a lower coefficient of variation in electrocardiographic R-R intervals than 10 age-matched controls (Murata et al. 1993). Significant deficits in 28 of 30 neurobehavioral tests were found for a group of electronics workers exposed to TWA concentrations of 88 ppm toluene for an average of 6 years compared with unexposed controls (Foo et al. 1990). Boey et al. (1997) also found significant deficits in neurological tests for electronics workers (exposed to TWA concentrations of 90.9 ppm toluene) compared with unexposed controls. Orbaek and Nise (1989) reported increased neurasthenic symptoms and performance deficits in psychometric tests for printers from two plants exposed to toluene for 4–43 years (median 29 years). At the time of the study (1985), TWA levels in the two plants were 11.4 and 41.7 ppm, but previous concentrations were higher, with estimated midpoints for each plant of 132 and 147 ppm and the mean of these midpoints, 140 ppm, can be taken as a representative exposure

concentration for the overall group. In general, these studies corroboratively demonstrate that subtle neurological effects can occur from repeated exposure to toluene concentrations within the range of 32–150 ppm.

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ]Intermediate [ ] Chronic
Key to figure: 10
Species: rat

MRL: 0.8 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Dyer RS, Bercegeay MS, Mayo LM. 1988. Acute exposures to *p*-xylene and toluene alter visual information processing. Neurotoxicol Teratol 10: 147–153.

Experimental design: Male Long-Evans rats (12 per group) were administered doses of toluene in corn oil of 0, 250, 500, and 1,000 mg/kg/day by gavage. Flash-evoked potential tests were administered 45 minutes later as a test of the ability of the nervous system to process visual information. In another study (time-course), toluene was administered to male Long-Evans rats (16 per group) at doses of 0 and 500 mg/kg/day by gavage and flash-evoked potential tests were performed 4, 8, 16, and 30 hours later.

Effects noted in study and corresponding doses: The amplitude of the N3 peak of the flash-evoked potential was significantly decreased ($P<0.05$) by toluene exposure at all doses. This decrease in peak amplitude was not dose-related. In the time course study, 500 mg/kg/day also decreased the amplitude of the flash-evoked potential; at this dose, little change in magnitude of peak N3 depression had occurred 8 hours post treatment; by 16 hours recovery was complete.

Dose endpoint used for MRL derivation: 250 mg/kg/day for neurological effects

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [x] 3 [ ] 10 (for use of a minimal LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

MRL = 250 mg/kg/day ÷ 300 = 0.8 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

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

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Although no additional acute oral animal studies are available on the neurological effects of toluene, a number of animal inhalation studies have reported neurological effects from toluene (Arito et al. 1988; Bushnell et al. 1994; Carpenter et al. 1986; Harabuchi et al. 1993; Hinman 1987). Human inhalation studies have shown the central nervous system to be the major end point for toluene exposure (Andersen et al. 1983; Baelum et al. 1985; Escheverria et al. 1991; Rahill et al. 1996).

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X]Intermediate [ ] Chronic
Key to figure: 29
Species: mouse

MRL: 0.02 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Hsieh GC, Sharma RP, Parker RDR et al. 1990b. Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. Ecotox Environ Safety 20: 175–184.

Experimental design: Male CD-1 mice (5 per group) were administered toluene in their drinking water for a 28-day period. Based on water consumption and average toluene concentrations, the authors calculated toluene doses for the four treatment doses of 0, 5, 22, and 105 mg/kg/day over this period. Brain levels of norepinephrine, dopamine, serotonin, 3-methoxy-4-hydroxymandelic acid, 3,4-dihydroxyphenylacetic acid, homovanillic acid, and 5-hydroxyindolacetic acid were measured in six areas of the brain in the mice. A level of $P<0.05$ was considered statistically significant unless otherwise stated.

Effects noted in study and corresponding doses: Significant increases in norepinephrin were present in the hypothalamus and in the midbrain in groups treated with 5, 22, and 105 mg/kg/day toluene. Toluene also increased serotonin levels, with the increase being maximal at 22 mg/kg/day in the midbrain ($P<0.005$) and cerebral cortex ($P<0.005$). A significant increase was also seen in the hypothalamus with norepinephrine, dopamine, and serotonin ($P<0.005$). In the corpus striatum, the levels of dopamine and serotonin were significantly increased at the two highest doses. In the medulla oblongata, significant toluene increases of norepinephrine and homovanillic acid were seen only at 22 mg/kg/day.

Dose endpoint used for MRL derivation: 5 mg/kg/day for neurological effects

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [x] 3 [ ] 10 (for use of a minimal LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

MRL = 5 mg/kg/day ÷ 300 = 0.02 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

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

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: The effects reported in the Hsieh et al. (1990b) study are minimal effects, and it is unclear how they are related to neurobehavioral changes. These results support the possible involvement of monoamine metabolism in the reported behavioral and neurophysiological effects of toluene. Alterations in the brain concentrations of neurotransmitters and their metabolites have been correlated with abnormal behavioral and physiological functions.

Although no additional intermediate oral animal studies are available on the neurological effects of toluene, a number of animal inhalation studies have reported neurological effects from toluene (Arito et al. 1988; Bushnell et al. 1994; Carpenter et al. 1986; Harabuchi et al. 1993; Hinman 1987). Human inhalation studies have shown the central nervous system to be the major endpoint for toluene exposure (Andersen et al. 1983; Baelum et al. 1985; Escheverria et al. 1991; Rahill et al. 1996).

An additional study that lends support to the MRL is a developmental study in which impaired rotorod performance and motor coordination were reported in the offspring of mice exposed to 4, 21, and 106 mg/kg/day (Kostas and Hotchin 1981). Pregnant mice were exposed to toluene in their drinking water throughout pregnancy and lactation. From weaning at 21 days of age until postnatal day 55, the pups were exposed to toluene in their drinking water. The dose levels received by the pups cannot be accurately determined because the exposure occurred in utero, during lactation, and also via drinking water. The neurobehavioral effects reported in the offspring support the MRL; however, the impairment of rotorod performance was not dose-related.

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and Figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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

LEGEND

See LSE Table 2-1

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

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

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

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

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

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

(10) Reference The complete reference citation is given in Chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious

effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

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

LEGEND

See Figure 2-1

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

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

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

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

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

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

SAMPLE

1 6

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

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

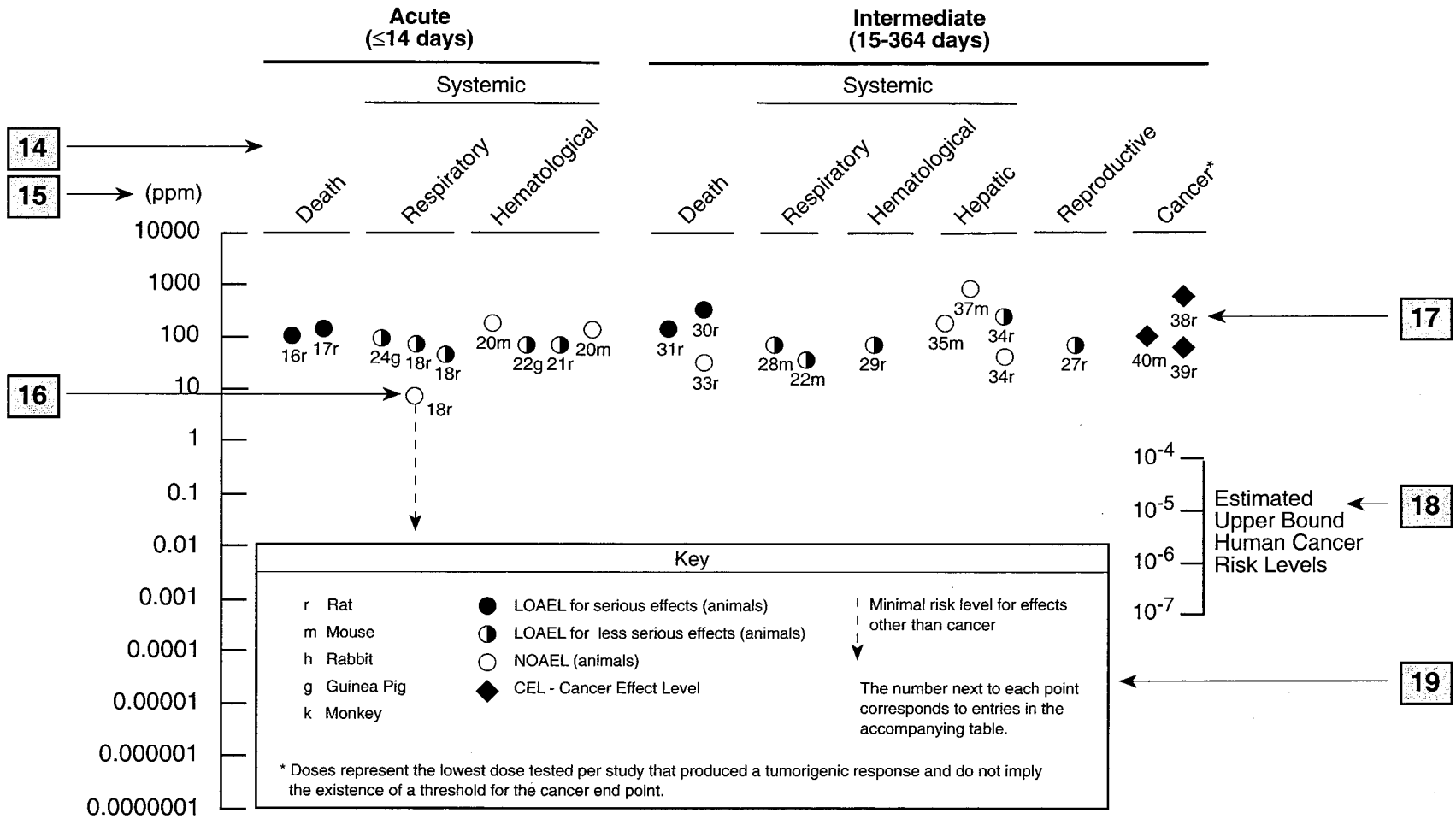
[a] The number corresponds to entries in Figure 2-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

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



Chapter 2 (Section 2.5)

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
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
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
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/IMCO	Department of Transportation/United Nations/ North America/International 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
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
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
PID	photo ionization detector

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard 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 Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

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

µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result