

TOXICOLOGICAL PROFILE FOR TRICHLOROBENZENES

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Trichlorobenzene, Draft for Public Comment was released in September 2010. This edition supersedes any previously released draft or final profile.

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

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FOREWORD

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

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

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

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

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



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*Legislative Background

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

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

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

Chapter 1	How Can (Chemical X) Affect Children?
Chapter 1	How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7	Children's Susceptibility
Section 6.6	Exposures of Children

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

Internet: <http://www.atsdr.cdc.gov>

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

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.

Clinical Resources

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

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

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. Ralph L. Kodell, Ph.D., Professor, Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, Arkansas;
2. Richard J. Bull, Ph.D., President, MoBull Consulting, Richland Washington; and
3. James E. Klaunig, Ph.D., Professor and Chair, Department of Environmental Health, School of Public Health, Indiana University at Bloomington, Indiana.

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

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

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

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CONTENTS

DISCLAIMER	ii
UPDATE STATEMENT	iii
FOREWORD	v
QUICK REFERENCE FOR HEALTH CARE PROVIDERS.....	vii
CONTRIBUTORS	ix
PEER REVIEW	xi
CONTENTS.....	xiii
LIST OF FIGURES	xvii
LIST OF TABLES	xix
1. PUBLIC HEALTH STATEMENT FOR TRICHLOROENZENES.....	1
2. RELEVANCE TO PUBLIC HEALTH	11
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TRICHLOROENZENES IN THE UNITED STATES	11
2.2 SUMMARY OF HEALTH EFFECTS.....	12
2.3 MINIMAL RISK LEVELS (MRLs).....	15
3. HEALTH EFFECTS	31
3.1 INTRODUCTION.....	31
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	31
3.2.1 Inhalation Exposure	32
3.2.1.1 Death	32
3.2.1.2 Systemic Effects.....	32
3.2.1.3 Immunological and Lymphoreticular Effects	49
3.2.1.4 Neurological Effects	50
3.2.1.5 Reproductive Effects.....	50
3.2.1.6 Developmental Effects	51
3.2.1.7 Cancer	51
3.2.2 Oral Exposure	51
3.2.2.1 Death	51
3.2.2.2 Systemic Effects.....	52
3.2.2.3 Immunological and Lymphoreticular Effects	90
3.2.2.4 Neurological Effects	90
3.2.2.5 Reproductive Effects.....	91
3.2.2.6 Developmental Effects	92
3.2.2.7 Cancer	93
3.2.3 Dermal Exposure.....	94
3.2.3.1 Death	94
3.2.3.2 Systemic Effects.....	95
3.2.3.3 Immunological and Lymphoreticular Effects	105
3.2.3.4 Neurological Effects	106
3.2.3.5 Reproductive Effects.....	106
3.2.3.6 Developmental Effects	106
3.2.3.7 Cancer	106
3.3 GENOTOXICITY	107
3.4 TOXICOKINETICS.....	112

3.4.1	Absorption.....	113
3.4.1.1	Inhalation Exposure	113
3.4.1.2	Oral Exposure	113
3.4.1.3	Dermal Exposure.....	115
3.4.2	Distribution	115
3.4.2.1	Inhalation Exposure	115
3.4.2.2	Oral Exposure	115
3.4.2.3	Dermal Exposure.....	117
3.4.3	Metabolism	117
3.4.4	Elimination and Excretion	121
3.4.4.1	Inhalation Exposure	122
3.4.4.2	Oral Exposure	122
3.4.4.3	Dermal Exposure.....	124
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	124
3.5	MECHANISMS OF ACTION	125
3.5.1	Pharmacokinetic Mechanisms.....	125
3.5.2	Mechanisms of Toxicity.....	128
3.5.3	Animal-to-Human Extrapolations.....	128
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS.....	129
3.7	CHILDREN'S SUSCEPTIBILITY.....	130
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	133
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Trichlorobenzenes.....	134
3.8.2	Biomarkers Used to Characterize Effects Caused by Trichlorobenzenes.....	134
3.9	INTERACTIONS WITH OTHER CHEMICALS	134
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE.....	134
3.11	METHODS FOR REDUCING TOXIC EFFECTS	135
3.11.1	Reducing Peak Absorption Following Exposure	135
3.11.2	Reducing Body Burden.....	135
3.11.3	Interfering with the Mechanism of Action for Toxic Effects.....	136
3.12	ADEQUACY OF THE DATABASE	136
3.12.1	Existing Information on Health Effects of Trichlorobenzenes	136
3.12.2	Identification of Data Needs	140
3.12.3	Ongoing Studies.....	148
4.	CHEMICAL AND PHYSICAL INFORMATION.....	149
4.1	CHEMICAL IDENTITY	149
4.2	PHYSICAL AND CHEMICAL PROPERTIES	149
5.	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL.....	153
5.1	PRODUCTION	153
5.2	IMPORT/EXPORT	156
5.3	USE.....	156
5.4	DISPOSAL.....	157
6.	POTENTIAL FOR HUMAN EXPOSURE	159
6.1	OVERVIEW	159
6.2	RELEASES TO THE ENVIRONMENT.....	163
6.2.1	Air	164
6.2.2	Water.....	167
6.2.3	Soil.....	168

6.3	ENVIRONMENTAL FATE	169
6.3.1	Transport and Partitioning	169
6.3.2	Transformation and Degradation	172
6.3.2.1	Air	172
6.3.2.2	Water.....	172
6.3.2.3	Sediment and Soil	173
6.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	174
6.4.1	Air	174
6.4.2	Water.....	180
6.4.3	Sediment and Soil	181
6.4.4	Other Environmental Media.....	181
6.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	185
6.6	EXPOSURES OF CHILDREN.....	186
6.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	187
6.8	ADEQUACY OF THE DATABASE	187
6.8.1	Identification of Data Needs	188
6.8.2	Ongoing Studies.....	190
7.	ANALYTICAL METHODS	191
7.1	BIOLOGICAL MATERIALS.....	191
7.2	ENVIRONMENTAL SAMPLES	193
7.3	ADEQUACY OF THE DATABASE	195
7.3.1	Identification of Data Needs	195
7.3.2	Ongoing Studies.....	196
8.	REGULATIONS, ADVISORIES, AND GUIDELINES.....	197
9.	REFERENCES	205
10.	GLOSSARY	221
APPENDICES		
A.	ATSDR MINIMAL RISK LEVELS AND WORKSHEETS	A-1
B.	USER'S GUIDE.....	B-1
C.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS.....	C-1
D.	INDEX	D-1

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LIST OF FIGURES

3-1. Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation	39
3-2. Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Inhalation.....	44
3-3. Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral.....	67
3-4. Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral.....	74
3-5. Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral.....	80
3-6. Hypothesized Metabolic Pathways for Trichlorobenzene Isomers Through Arene Oxide Intermediates.....	119
3-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance.....	126
3-8. Existing Information on Health Effects of 1,2,3-Trichlorobenzene	137
3-9. Existing Information on Health Effects of 1,2,4-Trichlorobenzene	138
3-10. Existing Information on Health Effects of 1,3,5-Trichlorobenzene	139
6-1. Frequency of NPL Sites with 1,2,3-Trichlorobenzene Contamination.....	160
6-2. Frequency of NPL Sites with 1,2,4-Trichlorobenzene Contamination.....	161
6-3. Frequency of NPL Sites with 1,3,5-Trichlorobenzene Contamination.....	162

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LIST OF TABLES

2-1. Summary of End Points Modeled in 13-Week Studies	24
2-2. Incidence of Liver Lesions in Rats in a 104-Week Dietary Study	26
3-1. Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation.....	34
3-2. Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Inhalation.....	42
3-3. Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral.....	53
3-4. Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral.....	70
3-5. Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral.....	76
3-6. Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Dermal.....	96
3-7. Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Dermal.....	101
3-8. Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Dermal.....	102
3-9. Genotoxicity of Trichlorobenzenes <i>In Vitro</i>	108
3-10. Genotoxicity of Trichlorobenzenes <i>In Vivo</i>	111
4-1. Chemical Identity of Trichlorobenzenes	150
4-2. Physical and Chemical Properties of Trichlorobenzenes	151
5-1. Facilities that Produce, Process, or Use 1,2,4-Trichlorobenzene	154
6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,2,4-Trichlorobenzene	165
6-2. Emissions of 1,2,4-Trichlorobenzene in 2011	166
6-3. Measured Bioconcentration Factors (BCF) of Trichlorobenzenes in Carp	170
6-4. 1,2,4-Trichlorobenzene Air Levels at Monitoring Stations Throughout the United States in 2008.....	175
6-5. The Range and Mean Concentration of Trichlorobenzene Isomers in Sediment Samples Obtained From the Great Lakes	182
6-6. Trichlorobenzene Concentrations in Whole Vegetables	184
7-1. Analytical Methods for Determining Trichlorobenzenes in Biological Samples.....	192

7-2. Analytical Methods for Determining Trichlorobenzenes in Environmental Samples.....	194
8-1. Regulations, Advisories, and Guidelines Applicable to Trichlorobenzenes.....	198

1. PUBLIC HEALTH STATEMENT FOR TRICHLOROBENZENES

Overview

We define a public health statement and show how it can help you learn about trichlorobenzenes.

Introduction

A public health statement summarizes information about a hazardous substance. The information is taken from a toxicological profile developed by the Agency for Toxic Substances and Disease Registry's (ATSDR's) Division of Toxicology and Human Health Sciences (DTHHS). A toxicological profile is a thorough review of a hazardous substance.

This toxicological profile examines trichlorobenzenes. This public health statement summarizes the DTHHS's findings on trichlorobenzenes, describes the effects of exposure to them, and describes what you can do to limit that exposure.

Trichlorobenzenes at hazardous waste sites

The U.S. Environmental Protection Agency (U.S. EPA) identifies the most serious hazardous waste sites in the nation. U.S. EPA then includes these sites in the National Priorities List (NPL) and targets them for federal clean-up activities. U.S. EPA has found 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene in at least 31, 187, and 4 of the 1,699 current or former NPL sites, respectively.

The total number of NPL sites evaluated for trichlorobenzenes is not known. But the possibility remains that as more sites are evaluated, the number of sites at which trichlorobenzenes is found may increase. This information is important; these future sites may be sources of exposure, and exposure to trichlorobenzenes may be harmful.

Why a trichlorobenzenes release can be harmful

When a contaminant 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. But such a release does not always lead to exposure. You can only be exposed to a contaminant when you come in contact with it. That contact—and therefore that exposure—can occur when you breathe, eat, or drink the contaminant, or when it touches your skin.

Even if you are exposed to trichlorobenzenes, you might not be harmed. Whether you are harmed will depend on such factors as the dose (how much), the duration (how long), and how you are exposed. Harm might also depend on whether you have been exposed to any other chemicals, as well as your age, sex, diet, family traits, lifestyle, and state of health.

1. PUBLIC HEALTH STATEMENT

A Closer Look at Trichlorobenzenes

Overview

This section describes trichlorobenzenes in detail and how you can be exposed to them.

What are trichlorobenzenes?

Trichlorobenzenes are human-made compounds that occur in three different chemical forms. Although they have the same molecular weight and molecular formula, they differ structurally by where the chlorine atoms are attached to the benzene ring. Compounds like these are referred to as isomers. Drawings of the three different isomers are shown in Chapter 4. 1,2,3-Trichlorobenzene and 1,3,5-trichlorobenzene are colorless solids, while 1,2,4-trichlorobenzene is a colorless liquid.

Although the three isomers of trichlorobenzene are structurally similar, they each may have different chemical and toxicological properties.

How are trichlorobenzenes used?

Trichlorobenzenes have primarily been used as solvents and chemical intermediates to produce other compounds. In the past, mixed isomers of trichlorobenzene had been used for termite control, but this is not a current use. One of the isomers (1,2,4-trichlorobenzene) is produced in large quantities and is used as a solvent to dissolve such special materials as oils, waxes, resins, greases, and rubber. It is also frequently used to produce dyes and textiles. The other two isomers, 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene, are produced in lower quantities and have fewer uses.

Where are trichlorobenzenes found?

Trichlorobenzenes can be released into the air, water, and soil at places where they are produced or used.

Possible Sources	Outcome
Air	Trichlorobenzenes are volatile substances and may therefore partition or volatilize to air when released to the environment. The half-life (the time it takes for 50% of the compound to degrade) of trichlorobenzenes in air is about 1 month.
Water	Trichlorobenzenes have been detected in groundwater, drinking water, and surface water (rivers and lakes). Trichlorobenzenes have a tendency to evaporate over time from water, but can also adsorb to suspended solids and sediment in water.
Soil	Trichlorobenzenes evaporate from soils and are slowly broken down by microorganisms in soil and sediment.

1. PUBLIC HEALTH STATEMENT

Other Media	Trichlorobenzenes in water and soil may be absorbed or ingested by animals, including fish. Trichlorobenzenes are often detected in the fat of fish or other species living in contaminated waters. This is because trichlorobenzenes can easily dissolve in fat; consequently, fish can accumulate trichlorobenzenes in fatty tissues.
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How Trichlorobenzenes Can Affect Your Health

Overview

This section looks at how trichlorobenzenes enter your body and potential trichlorobenzenes health effects found in human and animal studies.

How trichlorobenzenes enter your body

Trichlorobenzenes can enter your body from the air, water, or soil.

Possible Sources	Possible Exposure Pathway
Air	<p>There is not enough information to determine how much or how fast trichlorobenzenes can be absorbed by your body if you inhale vapors or contaminated air.</p> <p>A study in rats indicated that trichlorobenzenes can be absorbed by the body through the lungs. However, we do not know how fast or how much can be absorbed.</p>
Water	<p>We do not know enough to determine how much or how fast trichlorobenzenes can be absorbed by your body if you swallow these chemicals.</p> <p>Studies in animals indicate that these chemicals can be quickly absorbed through the gastrointestinal tract.</p>
Soil	<p>We do not know whether trichlorobenzenes can be absorbed through your skin if you touch soil containing these chemicals.</p> <p>Studies in animals have shown that some 1,2,4-trichlorobenzene can be absorbed through the skin.</p>

1. PUBLIC HEALTH STATEMENT

What happens to trichlorobenzenes in your body There is no information regarding what happens to trichlorobenzenes in humans. In animals, trichlorobenzenes are transformed in the body into other chemicals.

How trichlorobenzenes leave your body There is no information on how these compounds could leave the body in humans, but based on studies in animals, they probably leave principally in the urine.

In animals, degradation products of trichlorobenzenes leave the body in the urine, feces, and bile in a few days following exposure.

Studies in animals suggest that trichlorobenzenes do not accumulate in the body of mammals, but can accumulate in fish to some extent.

Introduction to trichlorobenzenes health effects The health effects of trichlorobenzenes depend on how much of these compounds you are exposed to and the length of that exposure. Environmental monitoring data suggest that any trichlorobenzene's levels that the public might encounter through contact or through water, soil, or food are much lower than animal-study levels.

Short-term exposure effects There is no information regarding health effects of trichlorobenzenes in humans other than reports of minimal eye and throat irritation in certain people exposed to vapors of 1,2,4-trichlorobenzene.

Placing trichlorobenzenes on the skin or the eyes of animals produced irritation that eventually went away after time.

Long-term exposure effects Very limited information exists regarding effects of long-term exposure in humans. There is a report of a woman who developed a blood disorder due to prolonged inhalation of trichlorobenzenes from her husband's work clothes.

Prolonged administration of 1,2,4-trichlorobenzene to rats did not affect their capacity to reproduce.

Trichlorobenzenes and cancer There are no studies of cancer in humans exposed to trichlorobenzenes.

Mice given 1,2,4-trichlorobenzene in the food for 2 years developed cancer of the liver.

The EPA has stated that 1,2,4-trichlorobenzene is not classifiable as to human carcinogenicity. However, this was based on studies prior to 1990; newer information has not been evaluated.

See Chapters 2 and 3 for more information on health effects of trichlorobenzenes.

1. PUBLIC HEALTH STATEMENT

Children and Trichlorobenzenes

Overview

This section discusses potential health effects of trichlorobenzenes exposure in humans from when they're first conceived to 18 years of age, and how you might protect against such effects.

Exposure effects for children

There are no studies of children exposed to trichlorobenzenes. Therefore, we do not know whether children are more susceptible than adults to the effects of exposure to trichlorobenzenes.

What about birth defects?

We do not know whether exposure of women to trichlorobenzenes during pregnancy can produce birth defects in their babies.

For the most part, studies in rats and mice given 1,2,4-trichlorobenzene orally during pregnancy did not cause effects in their pups at birth or later during the growing period. However, a study in rats found lesions in the eyes of the pups.

Breast milk

Trichlorobenzenes have been found in human breast milk, which means that mothers can transfer these chemicals to their babies by nursing.

How Can Families Reduce the Risk of Exposure to Trichlorobenzenes?

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

Food

Trichlorobenzenes tend to accumulate in the fatty tissue of fish; therefore, avoid eating large quantities of fish from areas contaminated with trichlorobenzenes. Avoid consumption of food crops grown in areas contaminated with trichlorobenzenes.

Drinking water

Avoid drinking water from sources that are known to be contaminated with trichlorobenzenes. Use bottled water if you have concerns about the presence of chemicals in your tap water. You may also contact local drinking water authorities and follow their advice.

1. PUBLIC HEALTH STATEMENT

Contaminated groundwater or soil Trichlorobenzenes have been detected in groundwater. Avoid contact with groundwater known to be contaminated with trichlorobenzenes.

Prevent children from playing in dirt if you live near a waste site that has trichlorobenzenes. Discourage your children from putting objects in their mouths. Make sure that they wash their hands frequently and before eating.

Medical Tests to Determine Trichlorobenzenes Exposure

Overview

We identify medical tests that can detect whether trichlorobenzenes are in your body, and we recommend safe toxic-substance practices.

Trichlorobenzenes can be measured in blood and body fat

Trichlorobenzenes can be measured in blood and body fat, but the tests are not routinely available at the doctor's office. The detection of trichlorobenzenes cannot predict the kind of health effects that might develop from that exposure.

There is not enough information to determine whether trichlorobenzenes detected in your body indicate that you have been exposed recently to a high amount or you are continuously exposed to lower amounts.

Detecting trichlorobenzenes in your body generally means that you were exposed to these compounds. However, detecting breakdown products of trichlorobenzenes may mean that you were exposed to trichlorobenzenes or that you were exposed to other chemicals that produce the same breakdown products.

For more information on the different substances formed by trichlorobenzenes breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

Federal Government Recommendations to Protect Human Health

Overview

One way the federal government promotes public health is by regulating toxic substances or recommending ways to handle or to avoid toxic substances.

The federal government regulates toxic substances

Regulations are enforceable by law. The U.S. EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that have adopted toxic substances regulations.

1. PUBLIC HEALTH STATEMENT

The federal government recommends safe toxic substance practices

The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) have made recommendations about toxic substances. Unlike enforceable regulations, these recommendations are advisory only.

Toxic substance regulations

Regulations and recommendations can be expressed as “not-to-exceed” levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

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

Some regulations and recommendations for trichlorobenzenes include:

Federal Organization	Regulation or Recommendation
U.S. Environmental Protection Agency (U.S. EPA)	<p>The EPA has determined that exposure to 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene in drinking water at concentrations of 0.1 and 0.6 milligrams per liter (mg/L), respectively, for 1 or 10 days is not expected to cause any adverse effects in a child.</p> <p>The EPA has determined that lifetime exposure to 0.07 mg/L 1,2,4-trichlorobenzene and 0.04 mg/L 1,3,5-trichlorobenzene is not expected to cause any adverse effects.</p> <p>EPA established a maximum contaminant level (MCL) of 0.07 mg/L for 1,2,4-trichlorobenzene in drinking water.</p>
Occupational Safety and Health Administration (OSHA)	OSHA has not established regulations for workers exposed to trichlorobenzenes.

1. PUBLIC HEALTH STATEMENT

National Institute for Occupational Safety and Health (NIOSH)	NIOSH considers 1,2,4-trichlorobenzene hazardous to the eyes, skin, respiratory system, liver, and reproductive system and established a recommended exposure limit (REL) of 5 ppm (concentration that should not be exceeded during any part of the working exposure).
Food and Drug Administration (FDA)	The FDA has determined that the concentration of 1,2,4-trichlorobenzene in bottled drinking water should not exceed 0.07 mg/L.

Additional Information

Overview

Where to find more information about trichlorobenzenes.

Who to contact If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

Additional information from ATSDR ATSDR can provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

Where to obtain toxicological profile copies Toxicological profiles are also available online at www.atsdr.cdc.gov. For more information:

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or
- Write to:

Agency for Toxic Substances and Disease Registry
 Division of Toxicology and Human Health Sciences
 1600 Clifton Road NE
 Mailstop F-57
 Atlanta, GA 30333

1. PUBLIC HEALTH STATEMENT

For-profit organizations should request final toxicological profile copies from:

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

1. PUBLIC HEALTH STATEMENT

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TRICHLOROBENZENES IN THE UNITED STATES

The manufacture and use of trichlorobenzenes as solvents, chemical intermediates, and dye carriers has led to their release into the environment. Trichlorobenzenes may also be released into the environment indirectly from the degradation of higher chlorinated benzenes (tetrachlorobenzene, pentachlorobenzene, and hexachlorobenzene) and the pesticide lindane (γ -hexachlorocyclohexane). They may also be present as a minor impurity in other chlorinated substances and are formed unintentionally during the combustion of organic materials when chlorine is present (for example during the incineration of wastes containing polyvinyl chloride).

Trichlorobenzenes are volatile substances that are relatively persistent in the environment. They are expected to possess low mobility in soil and generally do not leach into groundwater except in the case of a large spill or their subsurface disposal at hazardous waste sites. Volatilization is considered an important environmental fate process in soils and water; however, their tendency to adsorb to soil and sediment may attenuate the rate of volatilization. In the atmosphere, trichlorobenzenes degrade through their reaction with photochemically-generated hydroxyl radicals. The half-life for this reaction in air is approximately 16–38 days. In soil and water, trichlorobenzenes degrade slowly under aerobic conditions but undergo reductive dechlorination resulting in the formation of mono- and dichlorobenzenes as degradation products under methanogenic conditions.

1,2,4-Trichlorobenzene is one of 188 chemicals that is designated as a hazardous air pollutant (HAP) under the Clean Air Act. Monitoring data from 2008 indicate that average atmospheric levels in the United States are typically less than 1 part per billion by volume (<1 ppbv); however, maximum levels above 3 ppbv have been observed. In atmospheric samples, 1,2,3- and 1,3,5-trichlorobenzene are detected less frequently than 1,2,4-trichlorobenzene since they have fewer uses and subsequently fewer direct emissions. Trichlorobenzenes are detected infrequently in groundwater unless a large spill occurs to a soil surface. Both 1,2,3- and 1,2,4-trichlorobenzene were monitored for, but not detected in, aquifer samples in a comprehensive survey conducted by the U.S. Geological Survey (USGS) of volatile organic compounds in private and public groundwater wells used for drinking water. Neither isomer was detected in samples obtained from nearly 2,000 public and private wells across the United States. Municipal drinking water samples have occasionally been shown to contain low levels of trichlorobenzenes at the

2. RELEVANCE TO PUBLIC HEALTH

parts per trillion levels. Trichlorobenzenes have been detected in fish and wildlife, particularly in the vicinity of chemical manufacturing plants that produce chlorinated substances. They have also been detected in various food items. Leafy vegetables, fruits, milk, and eggs/meat purchased at grocery stores in Canada contained trichlorobenzene levels of 0.11–0.40, 0.12–0.14, 0.14–1.2, and 0.70–0.74 µg/kg, respectively.

The general population is exposed to trichlorobenzene from inhalation of ambient air and ingestion of food and drinking water. In a European Union Risk Assessment Report for 1,2,4-trichlorobenzene, the total daily intake was calculated as 0.0715 mg/kg/day for the exposure scenario which yielded the highest estimated total daily intake for humans. The estimates suggest that the most important human intake routes are ingestion of root crops, fish, and drinking water. Occupational exposure may occur through inhalation and dermal exposure where trichlorobenzenes are produced or used. Chapter 7 provides details of analytical methods used to determine whether exposure to trichlorobenzenes has occurred; however, not enough data are available to determine what baseline levels are in human tissues.

2.2 SUMMARY OF HEALTH EFFECTS

There is very limited information regarding health effects in humans following exposure to trichlorobenzenes. A review of the literature indicates that an adult male who inhaled trichlorobenzene for several hours during the repair of a pump suffered massive hemoptysis (blood-stained sputum), and that some trichlorobenzene production workers developed chloroacne. There is also a case report of aplastic anemia in a woman with prolonged exposure through the soaking of her husband's work clothes in trichlorobenzene. None of these reports provided exposure details or specified the isomer involved. Citing an unpublished source, the American Conference of Governmental Industrial Hygienists (ACGIH) stated that minimal eye and throat irritation could occur in some people exposed to 3–5 ppm 1,2,4-trichlorobenzene. This information is insufficient to determine a clear target for trichlorobenzenes in humans. However, based on information from effects of other chlorinated benzenes in humans, and from limited information on the metabolism of 1,2,4-trichlorobenzene by microsomal preparations from human livers that indicated that cytochrome P-450 enzymes might be involved in the metabolism of trichlorobenzenes, it is reasonable to suggest that excessive exposure to trichlorobenzenes might induce liver effects such as porphyria in humans.

Studies have been conducted in animals exposed to trichlorobenzenes by the inhalation, oral, and dermal routes. 1,2,4-Trichlorobenzene has been the most extensively studied of the three trichlorobenzene

2. RELEVANCE TO PUBLIC HEALTH

isomers. Repeated inhalation studies in multiple species exposed to up to 100 ppm 1,2,4-trichlorobenzene showed the liver to be a target, and rats appeared to be more sensitive than other species. Liver effects consisted mostly of increases in liver weight not accompanied by histological alterations. Exposure to 30 or 100 ppm 1,2,4-trichlorobenzene also increased the urinary excretion of porphyrins in rats. No target could be identified for 1,3,5-trichlorobenzene in rats in the only 13-week inhalation study located for this isomer. No inhalation data were located for 1,2,3-trichlorobenzene.

Trichlorobenzenes produced transitory irritation of the skin of animals when applied for short periods of time. As the duration of exposure increases, the severity of the effects also increases. Trichlorobenzenes also produced transitory eye irritation when instilled into the eyes of rabbits for short periods of time.

Considerable more data are available in animals exposed orally to trichlorobenzenes. Significantly more information is available for 1,2,4-trichlorobenzene than for the other two isomers. Acute-, intermediate-, and chronic-duration studies showed that the liver and kidneys are targets for 1,2,4-trichlorobenzene in rats. The liver was also the target for 1,2,4-trichlorobenzene in mice in an intermediate-duration study. Liver changes included increases in the weight of the organ and histological alterations consisting of periportal cytoplasmic eosinophilia and anisokaryosis (variation in size) of hepatocellular nuclei in acute-duration studies in rats dosed with ≥ 150 mg/kg/day 1,2,4-trichlorobenzene or ≥ 300 mg/kg/day 1,2,3- or 1,3,5-trichlorobenzene. Liver necrosis was reported in a 10-day study in rats dosed with 500 mg/kg/day 1,2,4-trichlorobenzene. Moderate liver histopathology was reported in rats dosed with ≥ 49 mg/kg/day of the trichlorobenzene isomers for 90 days. Extending the duration of exposure to 1,2,4-trichlorobenzene to 2 years resulted in increased incidences of various lesions including hepatocellular hypertrophy, focal cystic degeneration, and diffuse fatty change in rats. No chronic-duration studies were located with the other two trichlorobenzene isomers.

In addition to inducing morphological alterations in the liver, 1,2,4-trichlorobenzene has been shown to be a potent inducer of phase I and phase II metabolic enzymes. In addition, in rats, 1,2,4-trichlorobenzene induces δ -aminolevulinic acid (ALA) synthetase, the rate-limiting enzyme in the biosynthesis of heme, which is consistent with the development of porphyria in rats administered 1,2,4-trichlorobenzene. Studies by Kato and coworkers have shown that both the induction of drug-metabolizing enzymes and ALA synthetase are not due to 1,2,4-trichlorobenzene itself but to its metabolite, 2,3,5-trichlorophenyl methyl sulfone.

2. RELEVANCE TO PUBLIC HEALTH

Kidney lesions were observed in male rats dosed with 144 mg/kg/day 1,2,4-trichlorobenzene for 13 weeks. The lesions consisted of dilated tubules, granular casts, hyaline droplets, and papillary mineral deposition. Also increased was the incidence or severity of interstitial nephritis and regenerative tubular epithelium. These lesions, particularly the hyaline droplets, are consistent with a $\alpha_{2\mu}$ -globulin nephropathy induced by a variety of organic chemicals in male rats. The $\alpha_{2\mu}$ -globulin is not present in human kidneys; hence, this particular nephropathy has no significance for humans. Increased incidences of transitional renal cell hyperplasia and renal papilla mineralization were reported in male rats dosed with 66.5 mg/kg/day 1,2,4-trichlorobenzene for 104 weeks. This is also consistent with the occurrence of male-specific nephropathy. None of these lesions were seen in female rats or in mice. 1,3,5-Trichlorobenzene was also reported to induce renal lesions in rats in a 13-week study. The alterations were also consistent with the male-specific nephropathy and were characterized by eosinophilic inclusions, enlargement and anisokaryosis of the epithelial lining cells, and hyperplasia of renal tubular epithelial cells.

Less clear than the effects on the liver and on the kidneys of male rats are reported alterations on the thyroid of rats induced by trichlorobenzenes. The three trichlorobenzene isomers reportedly induced mild histological changes in the thyroid from pregnant female rats administered the chemicals on gestation days (Gd) 6–15 and sacrificed on Gd 22. The alterations occurred with doses ≥ 300 mg/kg/day and were characterized as reductions in follicle size and increased epithelial height accompanied by cytoplasmic vacuolization. Similar findings were reported in rats dosed with 78–82 mg/kg/day trichlorobenzenes for 13 weeks. However, neither study showed the data or provided quantitative analyses of the lesions that would have helped determine whether differences between dose groups were statistically significant. A 13-week study in rats that used comparable doses and a 104-week study in rats that provided quantitative data did not report treatment-related histological alterations in the thyroid. Intermediate- and chronic-duration studies in mice also did not report histological changes in the thyroid. None of these studies measured levels of thyroid hormones or thyrotrophin (TSH) in blood.

1,2,4-Trichlorobenzene did not affect fertility in rats in a multi-generation reproductive study. None of the intermediate-duration oral, inhalation, or dermal studies conducted with trichlorobenzenes reported treatment-related histological alterations in the reproductive organs of male and female animals. Most studies that examined whether 1,2,4-trichlorobenzene is a developmental toxicant reported negative results. The only effects reported were the presence of microscopic alterations in the lenses of the eye of fetuses from rats treated with 150 mg/kg/day 1,2,4-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22. However, no lesions were observed in fetuses from dams dosed with 75 or 300 mg/kg/day 1,2,4-trichloro-

2. RELEVANCE TO PUBLIC HEALTH

benzene. This lesion was also observed in fetuses from dams dosed with 150, 300, or 600 mg/kg/day 1,3,5-trichlorobenzene. Since no quantitative data were presented, it is not known whether the incidences were dose-related. The lesion was characterized as central areas of cellular disorientation and disaggregation with ballooning and granular degeneration. Another gestational exposure study reported retarded development of the fetuses from rats dosed with 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 and sacrificed on Gd 14. This dose level was lethal to two out of nine dams and induced significant weight loss in dams that survived. In studies of pregnant mice dosed with 0 or 130 mg/kg/day 1,2,4-trichlorobenzene on Gd 8–12, the chemical did not affect pup's viability or growth or offspring's locomotor activity or fertility to produce a second generation.

1,2,4-Trichlorobenzene did not significantly increase the incidence of malignancies in rats fed a diet that provided up to 66.5 mg/kg/day to males or 81.4 mg/kg/day to females. However, it did increase the incidence of hepatocellular carcinoma in mice fed a diet that provided ≥ 100.6 mg/kg/day to males and ≥ 127 mg/kg/day to females for 104 weeks. A dermal bioassay was also conducted with 1,2,4-trichlorobenzene in mice. Tumors developed in the lungs, kidneys, stomach, urinary bladder, mammary gland, and skin in both treated and control groups. Several limitations of this study rendered it inadequate for assessing the potential carcinogenicity of 1,2,4-trichlorobenzene following dermal exposure. EPA classified 1,2,4-trichlorobenzene in Group D: not classifiable as to human carcinogenicity, or as a chemical for which there is "Inadequate Information to Assess Carcinogenic Potential" according to the Guidelines for Carcinogen Risk Assessment. EPA's classification was done in 1988 and was last revised in 1991. No cancer studies were available for 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene.

2.3 MINIMAL RISK LEVELS (MRLs)

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

2. RELEVANCE TO PUBLIC HEALTH

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs***1,2,4-Trichlorobenzene***

Acute-Duration MRL. No relevant human data were located for 1,2,4-trichlorobenzene. The only data in animals is that exposure of rats (2–4/sex) to ≥ 70 ppm for 6 hours caused lethargy and initial lacrimation (Gage 1970), and that exposure of two rats to an average concentration of 293 ppm of 1,2,4-trichlorobenzene vapors 6 hours/day for 12 days did not cause gross or microscopic alterations in unspecified organs (E.I. Dupont 1971). This information is insufficient for MRL derivation.

Intermediate-Duration MRL. No relevant human data were located. Several intermediate-duration studies in various species are available. Continuous exposure of cynomolgous monkeys (9 males/group), Sprague-Dawley rats (30 males/group) rats, or New Zealand rabbits (16 males/group) to 0, 25, 50, or 100 ppm 1,2,4-trichlorobenzene vapors did not result in significant gross or microscopic appearance of the major organs at termination or in significant deviations in hematology or clinical chemistry tests conducted at various times during the study (Coate et al. 1977). Exposure-related histopathological changes characterized as mild (only qualitative descriptions were provided) were observed in the liver and kidneys from rats usually after 4 or 13 weeks of exposure, but not at week 26. Pulmonary function tests and operant behavior tests conducted in monkeys during the study were unremarkable. In another intermediate-duration study, exposure of Sprague-Dawley rats (20 males/group), beagle dogs (2 males/group), and New Zealand rabbits (4 males/group) to 0, 30, or 100 ppm 1,2,4-trichlorobenzene vapors 5 days/week for a total of 30 exposures did not result in gross or histological changes in any major tissues and organs, including the liver and kidneys (Kociba et al. 1981). Hematology and clinical chemistry tests also were unremarkable. The only significant changes in organ weights were an 11% increase in relative liver weight in rats and a 27–30% increase in absolute and relative liver weight in dogs. Increased urinary excretion of porphyrins was reported in exposed rats, which the investigators attributed to hepatic enzyme induction by 1,2,4-trichlorobenzene. In yet an additional intermediate-

2. RELEVANCE TO PUBLIC HEALTH

duration earlier study, Alderley Park rats (2–4/sex/group) were exposed 6 hours/day to 20 ppm 1,2,4-trichlorobenzene vapors for 20 exposures or to 70 or 200 ppm for 15 exposures (Gage 1970). Exposure to 70 or 200 ppm 1,2,4-trichlorobenzene produced lacrimation and lethargy, presumably during exposures, although it was not explicitly stated, but did not induce histological alterations in the lung, liver, heart, intestines, adrenals, spleen, or thymus. Although there is suggestive evidence from some studies that the liver might be a target for 1,2,4-trichlorobenzene, inadequacies in the studies (no quantitative data, only a few animals tested) preclude derivation of an intermediate-duration inhalation MRL for this isomer.

Chronic-Duration MRL. No chronic-duration inhalation studies were available in humans or animals for 1,2,4-trichlorobenzene; therefore, a chronic-duration inhalation MRL was not derived for this isomer.

1,2,3-Trichlorobenzene

No inhalation studies in humans or in animals were located for 1,2,3-trichlorobenzene; therefore, no inhalation MRLs were derived for this compound.

1,3,5-Trichlorobenzene

Acute-Duration MRL. No pertinent information in humans was located for 1,3,5-trichlorobenzene. The only acute data in animals is that head-only exposure of Sprague-Dawley rats (8/sex) for 60 minutes to 1,209 ppm 1,3,5-trichlorobenzene vapors appeared to cause some irritation around the eyes (Jorgenson et al. 1976). No clinical signs or mortality occurred during 14 days after the exposure, but exposed males and females weighed 44 and 60%, respectively, less than unexposed control rats. Gross necropsy did not reveal compound-related alterations. This information is inadequate for MRL derivation.

Intermediate-Duration MRL. Only one intermediate-duration inhalation study was located for 1,3,5-trichlorobenzene. In this study, male and female CD rats (20/sex/group) were exposed to 0, 1.3, 13, or 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983). A dried red material was often seen on the faces of rats during exposures, including controls, although the incidence was noticeably higher in the 13 and 130 ppm groups. Exposure to 1,3,5-trichlorobenzene had no significant effect on body weight or on hematology or clinical chemistry tests conducted at termination. Methemoglobin was slightly higher at week 13 than at week 4, but according to the investigators, the values did not reach significant levels (data not shown). Urinalyses performed on

2. RELEVANCE TO PUBLIC HEALTH

samples collected on weeks 4 and 13 showed an apparent increase in porphyrins in male rats on week 13, but the large standard deviations rendered the differences with controls nonsignificant. Relative liver weight was significantly increased (11%) in male rats on week 4 but not at termination. At termination, a total of 34 organs and tissues (not all specified) from the control and high-exposure group were examined microscopically, including the nasal passages. The only treatment-related histopathology was the presence of squamous metaplasia and hyperplasia in the respiratory epithelium of the nasal passages of three high-exposure rats (3/20); this incidence is not significantly different from controls (0/20) as determined by the Fisher Exact Test. The lack of clear effects precludes the use of this study for MRL derivation. The study NOAEL was the highest exposure concentration tested, 130 ppm, but the true NOAEL may have been higher.

Chronic-Duration MRL. No chronic-duration inhalation studies were available for 1,3,5-trichlorobenzene; therefore, a chronic-duration inhalation MRL was not derived for this isomer.

Oral MRLs**1,2,4-Trichlorobenzene**

Acute-Duration MRL. An acute-duration oral MRL was not derived for 1,2,4-trichlorobenzene due to inadequacies of the data base. No relevant human data were located. Other than acute lethality studies, the animal database consists of developmental studies in rats (Black et al. 1988; Kitchin and Ebron 1983) and mice (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986) and two studies aimed mainly at evaluating the effects of 1,2,4-trichlorobenzene on porphyrin metabolism (Rimington and Ziegler 1963), liver weight, and liver microsomal enzymes (Carlson and Tardiff 1976). These studies identified the liver as a target for 1,2,4-trichlorobenzene. In the study by Black et al. (1988), microscopic examination of the major tissues and organs from the dams exposed on Gds 6–15 and sacrificed on Gd 22 showed mild histological alterations in the liver and thyroid at doses of 300 mg/kg/day but not 150 mg/kg/day. However, the investigators provided only qualitative descriptions of the histological changes; incidences of lesions were not provided. Hemoglobin and hematocrit were decreased 6–7% in rats dosed with ≥ 150 mg/kg/day 1,2,4-trichlorobenzene relative to controls. This difference is not considered biologically significant since the values in treated rats were within the normal range. Rats dosed with 300 mg/kg/day 1,2,4-trichlorobenzene showed an 11% increase in relative liver weight; the investigators stated that absolute weight of rats dosed with 300 mg/kg/day was significantly increased but did not provide the values for the control group, and therefore the magnitude of the increase cannot be assessed. There were no significant effects on number of pregnancies, fetal weight, litter size, number of

2. RELEVANCE TO PUBLIC HEALTH

resorptions and dead fetuses, or incidences of skeletal or visceral anomalies. The only developmental effect reported was the presence of microscopic lesions in the lenses of the eyes of fetuses from dams treated with 150 mg/kg/day 1,2,4-trichlorobenzene; no such lesions were reported in groups dosed with 75 or 300 mg/kg/day. This study is inadequate for MRL derivation due to the lack of quantitative histology data, which precludes constructing dose-response relationships to determine points of departure for the MRL.

In the other developmental study in rats, pregnant animals were administered 0, 36, 120, or 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 and were sacrificed on Gd 14 (Kitchin and Ebron 1983). Rats that received the highest dose, 360 mg/kg/day, lost weight and had moderate hepatocellular hypertrophy (only the liver was examined microscopically); the no-observed-adverse-effect level (NOAEL) for these effects was 120 mg/kg/day. While doses of 360 mg/kg/day did not increase resorptions or cause significant embryolethality or teratogenicity, they significantly retarded fetal development as measured by reduced head length, crown-rump length, somite number, and protein content. These end points were evaluated only in dams administered 360 mg/kg/day 1,2,4-trichlorobenzene and controls, but not in groups dosed with 36 or 120 mg/kg/day 1,2,4-trichlorobenzene, which makes this study inadequate for MRL derivation because the NOAEL for weight loss and liver effects (120 mg/kg/day) may not be the NOAEL for retarded fetal development.

In the developmental studies in mice, pregnant mice were administered 0 or 130 mg/kg 1,2,4-trichlorobenzene on Gd 8–12 (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986). This treatment did not significantly affect offspring viability, reactive locomotor activity of the pups evaluated at various times up to 200 days of age, or reproductive performance of the offspring to produce a second generation. The use of only one dose level in these studies precludes constructing dose-response relationships for the end points measured. The lack of reported effects also precludes using this study for MRL derivation.

Rimington and Ziegler (1963) reported increased liver microsomal enzyme activities, increased urinary excretion of porphyrins, and also elevated levels of porphyrins in the liver of rats following daily gavage doses of 500 mg/kg/day for 10 days. The limited scope and single dose level precludes considering this study for MRL derivation. Carlson and Tardiff (1976) administered 1,2,4-trichlorobenzene in doses of 0, 10, 20, or 40 mg/kg/day to male rats by gavage in corn oil for 14 days. Sacrifices were conducted on day 15, and liver microsomal enzymes were analyzed. Blood was also collected for hemoglobin and hematocrit determinations. Sections of the liver were also prepared for histological examination.

2. RELEVANCE TO PUBLIC HEALTH

Administration of 1,2,4-trichlorobenzene resulted in dose-related increases in cytochrome c reductase, cytochrome P-450, glucuronyltransferase, EPN detoxification, and azoreductase. 1,2,4-Trichlorobenzene induced a dose-related increase in relative liver weight (all doses, 15% at the lowest dose, 28% at the highest dose). There were no significant effects on hemoglobin concentration or hematocrit. No specific information regarding liver histopathology was provided. Because the Carlson and Tardiff (1976) study is of limited scope and provided no information regarding histology of the liver, it is considered inadequate for MRL derivation.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 1,2,4-trichlorobenzene.

No relevant intermediate-duration studies in humans were located. The intermediate-duration oral database for 1,2,4-trichlorobenzene consists of two 3-month dietary studies in rats (CMA 1989; Côté et al. 1988), a 13-week dietary study in mice (Hiles 1989), two studies in rats aimed mainly at evaluating porphyrin metabolism and enzyme induction in the liver by 1,2,4-trichlorobenzene (Carlson and Tardiff 1976; Rimington and Ziegler 1963), and a multi-generation reproductive study in rats (Robinson et al. 1981). As a whole, these studies suggested that the liver and kidneys are targets for 1,2,4-trichlorobenzene and that male rats may be more sensitive than females. Administration of 730 mg/kg/day 1,2,4-trichlorobenzene (only dose level tested) by gavage to male albino rats caused intense necrosis and fatty change in the liver (only organ examined) and increased urinary porphyrins (Rimington and Ziegler 1963). Treatment of male albino rats via the diet with a much smaller dose, 40 mg/kg/day, increased relative liver weight (9–14%) and induced microsomal enzymes, but did not induce histological alterations in the liver (Carlson and Tardiff 1976).

In the multi-generation study, doses of up to 33 mg/kg/day in males and 54 mg/kg/day in females (mean doses estimated by the investigators consumed by 83 days of age F0 generation of rats) did not affect fertility in the F0 or F1 generation or affect the time of vaginal opening in F2 females (Robinson et al. 1981). Treatment with 1,2,4-trichlorobenzene did not affect neonates' weight, litter size, or viability during the pre-weaning period in any generation. Post-weaning growth of F1 rats was not affected by 1,2,4-trichlorobenzene. Tests for locomotor activity in the F1 or F2 generation rats were unremarkable. Of the organs weighed in the study (which included the liver and kidneys), only the adrenals were affected by 1,2,4-trichlorobenzene. Absolute weight of the adrenals of F0 and F1 males and females were significantly increased relative to controls (11–12% in F0 and 4–6% in F1); no histological evaluation of the glands was conducted. No histological damage was found in the livers and kidneys. Results from blood chemistry tests in F0 and F1 rats did not reveal any treatment-related alterations. The significance

2. RELEVANCE TO PUBLIC HEALTH

of the increase in adrenals weight is unknown. EPA (IRIS 2010) states that a 1-month study was performed by the Agency in which five rats/group were dosed by gavage with 53 mg/kg/day 1,2,4-trichlorobenzene in corn oil. Microscopic examination of the adrenals from treated rats showed moderate vacuolization of the zona fasciculata; the control group showed only slight vacuolization. A 14% increase in absolute adrenal gland weight and a 13% increase in relative adrenal weight were found. According to EPA (IRIS 2010, last revised 11/01/96), this study indicated that the increase in adrenal gland weight observed by Robinson et al. (1981) could be associated with vacuolization of the zona fasciculata. Since these observations are not supported by results from an acute-duration study (Black et al. 1988), two 3-month studies (CMA 1989; Côté et al. 1988), or a 104-week dietary study in rats, all of which conducted gross and microscopic evaluation of the adrenals from rats, the biological significance of the effects reported by Robinson et al. (1981) remains unclear. Since aside from the changes in adrenals weight, no adverse effect was identified in this multi-generation study, the study is considered inadequate for MRL derivation.

In the 13-week study in mice, groups of B6C3F₁ mice (10/sex/group) were administered a diet with 0, 220, 3,850, or 7,700 ppm 1,2,4-trichlorobenzene (Hiles 1989). The diet provided doses of 0, 67, 850, or 1,222 mg/kg/day to males and 0, 86, 1,183, or 1,345 mg/kg/day to females. End points monitored included clinical signs twice daily, and body weight and food consumption weekly. Hematology and clinical chemistry tests were conducted at initiation and during week 14. At termination, gross necropsy was conducted, selected organs were weighed, and selected tissues were examined microscopically. The lungs, liver, and kidneys from all groups were examined; other organs from only the control and high-dose groups were examined. Ophthalmologic examinations were conducted at initiation and termination. One control female and one high-dose female were accidentally killed during the study. Final body weight was significantly reduced in high-dose males (9%) and females (8.3%). Cumulative body weight gain was significantly reduced in low-dose males (27%), high-dose males (40%), and high-dose females (33%); these changes were associated with significant reductions in food consumption throughout the study. Significant, treatment-related alterations occurred only in the liver from males dosed with ≥ 850 mg/kg/day and females dosed with $\geq 1,183$ mg/kg/day; the respective NOAELs were 67 and 86 mg/kg/day. The lesions consisted of hepatocellular cytomegaly with karyomegaly and hepatocellular atrophy and degeneration. The incidences in males and females were 0/10, 0/10, 10/10, and 10/10 and 0/9, 0/10, 10/10, and 9/9, respectively.

One of the 3-month studies in Sprague-Dawley rats that evaluated hematology, clinical chemistry, and histopathology of the major organ and tissues reported histological alterations in the liver, kidneys, and

2. RELEVANCE TO PUBLIC HEALTH

thyroid in the various dose groups (doses ranged from 0.07 to 82 mg/kg/day in males and from 0.11 to 101 mg/kg/day in females) (Côté et al. 1988). However, the investigators provided only a qualitative description of the results, such that dose-response relationships for the histological changes could not be constructed. In that study, high-dose males showed increases of 13 and 20% in absolute and relative liver weight, respectively, and of 31 and 36% in absolute and relative kidneys weight, respectively.

Hematology and clinical chemistry tests were unremarkable. Because quantitative data regarding the histological effects were not presented, potential points of departure for the MRL could not be identified and the study is considered inadequate for MRL derivation.

In the 3-month study conducted by CMA (1989), groups of Fisher-344 rats (10/sex/group) were fed a diet containing 0, 200, 600, or 1,800 ppm 1,2,4-trichlorobenzene for 14 weeks; this diet provided doses of 0, 14.6, 45.6, or 133.7 mg/kg/day for males and 0, 17.0, 52.5, or 150.6 mg/kg/day for females. End points monitored included clinical signs (daily), physical examination (weekly), ophthalmology (initiation and termination), body weight and food consumption (weekly), hematology and clinical chemistry (termination), gross necropsy (all rats at termination), selected organ weights, and histopathology of all major organs and tissues of the control and high-dose group and liver and kidney of the low- and mid-dose groups. Treatment with 1,2,4-trichlorobenzene did not affect survival rate. Clinical signs were limited to chromodacryorrhea and lacrimation, which occurred more frequently in treated groups, but without dose-response. The test for ocular abnormalities did not reveal compound-related effects. Administration of 1,2,4-trichlorobenzene did not significantly affect body weight or weight gain. Food consumption was significantly higher in the mid- and high-dose groups than in controls. Significant hematological alterations consisted of decreased mean erythrocyte count (5%), hemoglobin (7%), and hematocrit (5%) in males dosed with 133.7 mg/kg/day and decreased hemoglobin (4%) and hematocrit (4%) in females dosed with 150.6 mg/kg/day. These changes are within the normal range and are not considered biologically significant. Platelets were significantly increased (16%) in males dosed with 133.7 mg/kg/day; the clinical significance of this finding is unclear; however, thrombocytosis is usually caused by a reaction to injury or inflammation. Significant clinical chemistry changes included elevated blood urea nitrogen (BUN) in high-dose males (12%) and females (20%), elevated total protein, albumin, and calcium in high-dose males, and lower serum aspartate aminotransferase (AST) activity in males dosed with 45.6 mg/kg/day (22%) and 133.7 mg/kg/day (28%). The elevated BUN was consistent with microscopic alterations in kidneys from male rats. The clinical significance of the alterations in protein and calcium were unclear and the lower transaminase activity was not considered of biological significance. Significant changes in organ weight included dose-related increases in absolute and relative liver weight in all treated male groups and in females dosed with 52.5 and 150.6 mg/kg/day, and

2. RELEVANCE TO PUBLIC HEALTH

increased absolute and relative kidney weight and absolute testes weight in males dosed with 133.7 mg/kg/day. No compound-related gross lesions were observed. Histological alterations were limited to the kidneys and liver. Kidney lesions were evident in males dosed with 45.6 and 133.7 mg/kg/day and consisted of dilated tubules, granular casts, hyaline droplets, interstitial nephritis, and papillary mineral deposition. In the liver, centrilobular hepatocyte hypertrophy occurred in males dosed with 45.6 and 133.7 mg/kg/day (0/10, 0/10, 5/10, and 10/10) and in females dosed with 150.6 mg/kg/day (0/10, 0/10, 0/10, and 10/10). Liver changes were more prominent in males than in females.

Both the 14-week study in rats by CMA (1989) and the 13-week study in mice by Hiles (1989) evaluated a comprehensive number of end points and presented the results in a manner useful for establishing dose-response relationships, and can potentially be used for MRL derivation.

Data sets of centrilobular hepatocyte hypertrophy in male rats and relative liver weights in male and female rats (CMA 1989), as well as hepatocyte atrophy and degeneration in male mice (Hiles 1989) were analyzed using the benchmark dose (BMD) approach for MRL derivation. Data for renal effects in male rats were not considered for modeling due to the strong suggestive evidence that this may be a unique response of the male rat and not relevant for human risk assessment (EPA 1991). Specific indications that this may be the case include the increased incidences of hyaline droplets, granular casts, and tubule dilation, and the fact that none of these lesions occurred in female rats. In addition, since there is not enough evidence to dissociate the interstitial nephritis from the male-specific nephropathy, interstitial nephritis was also not considered for modeling. In support of this position is the fact that interstitial nephritis did not occur in female rats.

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data sets for centrilobular hepatocyte hypertrophy in male rats and relative liver weights in male and female rats from the CMA (1989) study, as well as hepatocyte atrophy and degeneration in male mice from the Hiles (1989) study. A benchmark response (BMR) of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and the lower-bound confidence limits on the BMDs (BMDLs) associated with an extra risk of 10% are calculated for all models. For continuous data, in the absence of a clear criteria as to what level of change in organ weight should be considered adverse, the BMR was defined as a change in mean body weight gain equal to 1 standard deviation from the control mean (EPA 2000a). Adequate model fit is judged by three criteria: goodness-of-fit ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control)

2. RELEVANCE TO PUBLIC HEALTH

closest to the predefined BMR. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) is chosen. None of the models could provide an adequate fit for relative liver weight in female rats, but the lowest dose, 17.0 mg/kg/day, was a NOAEL. A summary of the modeling results is presented in Table 2-1.

Table 2-1. Summary of End Points Modeled in 13-Week Studies

End point	BMD _{1SD} /BMD ₁₀ (mg/kg/day)	BMDL _{1SD} /BMDL ₁₀ (mg/kg/day)	Best fitting model
Relative liver weight (male rats) ^a	11.27	9.41	Linear
Hepatocyte hypertrophy (male rats)^a	33.09	14.35	Gamma
Hepatocyte atrophy and degeneration (male mice) ^b	220.61	58.94	Gamma

^aCMA 1989

^bHiles 1989

Although Table 2-1 shows that the BMDL_{1SD} of 9.41 mg/kg/day for relative liver weight would be a slightly more protective point of departure for MRL derivation than the BMDL₁₀ of 14.35 mg/kg/day for hepatocyte hypertrophy in male rats, the latter is preferred as the point of departure on the basis of being a more biologically meaningful end point. The MRL is derived by dividing the BMDL₁₀ of 14.35 mg/kg/day for centrilobular hepatocyte hypertrophy by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). This yields an intermediate-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene. Detailed information regarding the modeling of hepatocyte hypertrophy in male rats is presented in Appendix A. Note that rounding to one decimal place would give the same MRL if based on relative liver weight.

- An MRL of 0.1 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to 1,2,4-trichlorobenzene.

No relevant chronic data in humans exposed orally to 1,2,4-trichlorobenzene were located, but there are 104-week dietary bioassays in rats (Moore 1994a) and in mice (Moore 1994b). In the study in rats, groups of Fisher-344 rats (50/sex/group) were fed a diet containing 0, 100, 350, or 1,200 ppm 1,2,4-trichlorobenzene for 104 weeks. The diet provided doses of 0, 5.6, 19.4, or 66.5 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 6.9, 23.5, or 81.4 mg/kg/day 1,2,4-trichlorobenzene to females. Parameters evaluated included mortality (twice daily), clinical signs, body weight and food consumption (weekly for 16 weeks and every 4 weeks thereafter), hematology (week 52 and 78 for cellular morphology and leukocyte differential, from control and high-dose groups), organ weight (at termination,

2. RELEVANCE TO PUBLIC HEALTH

brain, brainstem, liver, kidneys, testes, and epididymis), and gross necropsy and histological examination of all major organs and tissues at termination. Treatment with 1,2,4-trichlorobenzene resulted in a significant reduction in survival rate in males dosed with 66.5 mg/kg/day. Survival rate in the control, 5.6, 19.4, and 66.5 mg/kg/day males at week 104 were 84, 80, 84, and 60% respectively. There were no distinct or pronounced compound-related differences in clinical signs between treated and control groups. Differences in body weight between treated and control rats were <10% throughout the study. Food consumption was decreased 4–7% in treated groups relative to controls during the study. The only statistically significant hematology findings were a decrease in basophiles at week 52 and monocytes at week 105 in males dosed with 66.5 mg/kg/day, which the investigators considered minor. No evidence of leukemia was noted. Gross necropsy at termination showed increased incidence of liver and kidney abnormalities in males dosed with 19.4 and 66.5 mg/kg/day and a slight increase in incidence of uterine masses in treated females relative to controls; these changes were not discussed any further. Significant changes in organ weight were limited to an increase in absolute and relative liver weight in both male and female rats receiving the highest doses of 1,2,4-trichlorobenzene and a decrease in absolute and relative testes weight in males dosed with 5.6 and 19.4 mg/kg/day. Treatment-related histological alterations were restricted to the liver of males and females and to the kidneys of males and consisted of the following: hepatocellular hypertrophy, focal cystic degeneration, diffuse fatty change, transitional renal cell hyperplasia, and increased severity of chronic rat nephropathy in males. Incidences of liver lesions are presented in Table 2-2 (note that a smaller number of animals from the low-dose groups were examined for histopathology).

The incidences of transitional cell hyperplasia in the kidneys of male rats were as follows: 2/50, 0/19, 2/50, and 34/50 in males dosed with 0, 5.6, 19.4, and 66.5 mg/kg/day 1,2,4-trichlorobenzene, respectively. Since there is strong evidence from the 14-week study (CMA 1989) suggesting that the renal lesions in male rats may represent a male-specific response not relevant for MRL derivation and that renal cell hyperplasia reported in the 104-week study is a typical response seen in the male rat nephropathy, renal cell hyperplasia is not considered any further as a potential end point for MRL derivation.

In the study in mice, groups of B6C3F₁ mice (50/sex/group) were fed a diet containing 0, 150, 700, or 3,200 ppm 1,2,4-trichlorobenzene for 104 weeks (Moore 1994b). The diet provided doses of 0, 21, 100.6, or 519.9 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 26.3, 127, or 572.6 mg/kg/day 1,2,4-trichlorobenzene to females. End points monitored were the same as in the study in rats described above (Moore 1994a). The liver was the target for 1,2,4-trichlorobenzene in mice. The most significant effect was an

2. RELEVANCE TO PUBLIC HEALTH

increase incidence of hepatocellular carcinoma in mid- and high-dose mice (8/50, 5/50, 27/50, and 50/50 in males and 1/50, 1/50, 28/50, and 46/50 in females). Centrilobular hepatocytomegaly was also significantly increased in mid- and high-dose males (0/50, 0/50, 27/50, and 20/50). Since non-neoplastic effects were observed only at higher doses than in rats and carcinoma occurred at that same dose level, this study will not be considered any further for MRL derivation.

Table 2-2 shows that: (1) diffuse fatty change was significantly increased in males and females only at the highest dose; (2) focal cystic degeneration occurred at lower incidence in the low- and mid-dose males compared to controls, and was significantly increased only at the highest dose; (3) hepatocellular hypertrophy in female rats occurred at increased frequency only at the highest dose; and (4) only hepatocellular hypertrophy in male rats exhibited dose-response characteristics. Based on these facts, only the hepatocellular hypertrophy in male rats was considered for MRL derivation.

Table 2-2. Incidence of Liver Lesions in Rats in a 104-Week Dietary Study

Males				
Dose (mg/kg/day)	0	5.6	19.4	66.5
Hepatocellular hypertrophy	2/50 (4%)	1/26 (3.8%)	5/50 (10%)	30/50 (60%)
Focal cystic degeneration	9/50 (18%)	3/26 (11.5%)	4/50 (8%)	19/50 (38%)
Diffuse fatty change	5/50 (10%)	3/26 (11.5%)	5/50 (10%)	14/50 (28%)
Females				
Dose (mg/kg/day)	0	6.9	23.5	81.4
Hepatocellular hypertrophy	6/50 (12%)	5/25 (20%)	5/50 (10%)	37/50 (74%)
Diffuse fatty change	15/50 (30%)	6/25 (24%)	21/50 (42%)	30/50 (60%)

Source: Moore 1994a

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data set for hepatocellular hypertrophy in the liver of male rats. A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Adequate model fit is judged by three criteria: goodness-of-fit ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest AIC is chosen. The Multistage (2-degree) model provided the best fit for the data yielding a BMD_{10} of 23.25 mg/kg/day and a corresponding $BMDL_{10}$ of 13.33 mg/kg/day.

2. RELEVANCE TO PUBLIC HEALTH

The MRL is derived by dividing the BMDL₁₀ of 13.33 mg/kg/day for hepatocellular hypertrophy in male rats by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). This yields a chronic-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene. Detailed information regarding the modeling of hepatocellular hypertrophy in male rats is presented in Appendix A.

1,2,3-Trichlorobenzene

Acute-Duration MRL. An acute-oral MRL for 1,2,3-trichlorobenzene was not derived due to inadequacy of the available data. No human data were located for 1,2,3-trichlorobenzene. Only one acute-duration oral animal study was located for 1,2,3-trichlorobenzene. In that study, pregnant Sprague-Dawley rats (14/group) were administered 0, 150, 300, or 600 mg/kg/day 1,2,3-trichlorobenzene by gavage in corn oil on Gd 6–15 (Black et al. 1988). The dams were sacrificed on Gd 22 and the uterus and ovaries were removed. Dams were reweighed and the internal organs were weighed. In addition, blood was collected for hematology and clinical chemistry tests. Fetuses were examined grossly for birth defects and skeletal and visceral anomalies. Fetuses were also preserved for histological examinations. The major organs and tissues from the dams were examined microscopically. There were no treatment-related deaths and no clinical signs, but mean body weight of the high-dose group tended to be lower (data not shown). Organ weights were not significantly affected. Hemoglobin was reduced in the 300 and 600 mg/kg/day groups (6–7%) and hematocrit was reduced (~6%) in the 600 mg/kg/day groups. Given the magnitude of these hematological changes, the effects are not considered biologically significant since the values are within the normal range. No significant clinical chemistry effects were reported. Reported histological changes were limited to the kidneys, liver, and thyroid. However, the investigators provided only a qualitative description of the results; incidences of lesions were not provided. There were no significant effects on number of pregnancies, fetal weight, litter size, number of resorptions and dead fetuses, or incidences of skeletal or visceral anomalies. Histological examination of the fetuses did not reveal treatment-related alterations. The lack of a quantitative presentation of the results of the histological examination of the maternal tissues renders this study inadequate for MRL derivation because of the inability to inspect dose-response relationships.

Intermediate-Duration MRL. No intermediate-duration oral MRL was derived for 1,2,3-trichlorobenzene. No relevant human data were located. Only one intermediate-duration study was available for this compound (Côté et al. 1988). In that study, groups of Sprague-Dawley rats (10/sex/group) were fed a diet containing 0, 1, 10, 100, or 1,000 ppm 1,2,3-trichlorobenzene for 13 weeks. This diet provided doses

2. RELEVANCE TO PUBLIC HEALTH

of 0, 0.08, 0.78, 7.6, 78 mg/kg/day 1,2,3-trichlorobenzene to males and 0, 0.13, 1.3, 12, or 113 mg/kg/day to females. End points evaluated included body weight (weekly), food consumption (weeks 1, 4, 8, 12), urinalysis (weeks 4, 8, 12), and clinical signs (daily). At termination, the rats were necropsied and blood was collected for hematological and clinical chemistry testing. Hepatic microsomal aniline hydroxylase (AH), aminopyrine demethylase (APDM) activities, and liver protein content were also determined. Bone marrow from the femur was aspirated for cytological evaluation. All major tissues and organs were prepared for microscopic examination. There were no treatment-related deaths. Food consumption was not affected; body weight gain from high-dose males was reduced 10.2% relative to controls (only data for males shown). There were no significant alterations in hematology or clinical chemistry parameters, and urinalyses were unremarkable. No significant gross changes in tissues were reported. Statistically significant changes in organs weight were limited to increases in relative liver weight (14%) in males dosed with 78 mg/kg/day and in relative kidney weight in males dosed with 0.08 mg/kg/day (14%), 0.78 mg/kg/day (14%), and 78 mg/kg/day (21%). 1,2,3-Trichlorobenzene had no significant effect on the hepatic mixed function oxidase activities measured. For the most part, compound-related histopathology was reported as mild and was limited to the liver and thyroid of generally high-dose rats and appeared to be more severe in males. However, the investigators provided only a qualitative description of the histological examinations; incidences of lesions were not presented. In the liver, most treated groups showed mild-to-moderate increases in cytoplasmic volume and anisokaryosis of hepatocytes, mostly in perivenous and midzone areas. High-dose rats showed mild aggregated basophilia as well as mild widespread midzonal vacuolization due to fatty infiltration. Changes in the thyroid consisted of reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape, and reduced colloid density. Changes in the high-dose group varied from mild to moderate. The urinalyses were unremarkable. Since no dose-responses can be constructed with the histological data and since the increases in relative kidney weight in males were not accompanied by any histological changes, this study is considered inadequate for use as basis for MRL derivation.

Chronic-Duration MRL. No chronic-duration oral data in humans or in animals were located for 1,2,3-trichlorobenzene. Therefore, a chronic-duration oral MRL was not derived for this compound.

1,3,5-Trichlorobenzene

Acute-Duration MRL. No acute-duration oral MRL was derived for 1,3,5-trichlorobenzene due to inadequacies of the database. No relevant human data were located. The acute-duration oral database for 1,3,5-trichlorobenzene in animals is limited to information regarding acute lethal doses (Côté et al. 1988;

2. RELEVANCE TO PUBLIC HEALTH

Jorgenson et al. 1976) and a developmental study in rats (Black et al. 1988). In the developmental study, pregnant Sprague-Dawley rats (14/group) were administered 0, 150, 300, or 600 mg/kg/day 1,3,5-trichlorobenzene by gavage in corn oil on Gd 6–15. The dams were sacrificed on Gd 22 and the uterus and ovaries were removed. Dams were reweighed and the internal organs were also weighed. Blood was collected for hematology and clinical chemistry tests. Fetuses were examined grossly for birth defects and skeletal and visceral anomalies. Fetuses were also preserved for histological evaluations. The major organs and tissues from the dams were examined microscopically. There were no treatment-related deaths. There were no clinical signs, but mean maternal body weight gain in the high-dose group was 34% lower than controls. Food consumption data were not provided. Significant increases in relative liver weight were observed at 300 and 600 mg/kg/day (9 and 25%, respectively); the investigators also stated that absolute liver weights from rats in the 300 and 600 mg/kg/day groups were significantly increased but did not provide the values for the control group, and therefore, the magnitude of the changes cannot be assessed. Hemoglobin and hematocrit were reduced in the 600 mg/kg/day group (10–11%). This is not considered a biologically significant change since it is still within the normal range. Maternal histological changes were restricted to the kidneys, liver, and thyroid. However, only a qualitative description of the histological changes was provided; incidences of lesions were not presented. There were no significant effects on the number of pregnancies, fetal weight, litter size, number of resorptions and dead fetuses, or incidences of skeletal and visceral abnormalities. However, histological examination of the fetuses showed lesions in the lenses of the eyes of pups from all treated groups (150, 300, and 600 mg/kg/day). These changes consisted of central areas of cellular disorientation and disaggregation with ballooning and granular degeneration. The lack of quantitative histology data precludes the use of this study for MRL derivation.

Intermediate-Duration MRL. An intermediate-duration oral MRL for 1,3,5-trichlorobenzene was not derived due to inadequacy of the database. No relevant human studies were located. Only one intermediate-duration oral study in animals was available for 1,3,5-trichlorobenzene. In that study, groups of Sprague-Dawley rats (10/sex/group) were fed a diet containing 0, 1, 10, 100, or 1,000 ppm 1,3,5-trichlorobenzene for 13 weeks (Côté et al. 1988). This diet provided doses of 0, 0.08, 0.81, 7.7, and 82 mg/kg/day for males and 0, 0.13, 1.5, 17, and 146 mg/kg/day for females. End points evaluated included body weight (weekly), food consumption (weeks 1, 4, 8, 12), urinalysis (weeks 4, 8, 12), and clinical signs (daily). At termination, the rats were necropsied and blood was collected for hematological and clinical chemistry testing. Hepatic microsomal AH, APDM activities, and liver protein content were also determined. Bone marrow from the femur was aspirated for cytological evaluation. All major tissues and organs were prepared for microscopic examination. Gross observations did not reveal any

2. RELEVANCE TO PUBLIC HEALTH

significant treatment-related alterations. Significant changes in organs weight were limited to an increase in relative liver weight in males dosed with 82 mg/kg/day (11%), an increase in absolute kidney weight in males dosed with 0.81 and 7.7 mg/kg/day (~20%), and increases in relative kidney weight in males dosed with 0.81 (14%), 7.7 (25%), and 82 mg/kg/day (14%). There were no significant alterations in hematology or clinical chemistry parameters. 1,3,5-Trichlorobenzene had no significant effect on AH and APDM activities. For the most part, compound-related histopathology was mild and was limited to the liver, thyroid, and kidneys, generally high-dose rats, and appeared to be more severe in males. However, the investigators only provided a qualitative description of the histological changes; incidences of lesions were not presented. In the liver, most treated groups showed mild-to-moderate increase in cytoplasmic volume and anisokaryosis of hepatocytes mostly in perivenous and midzone areas. High-dose rats showed aggregated basophilia as well as widespread midzonal vacuolization due to fatty infiltration. Changes in the thyroid consisted of reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape, and reduced colloid density. Changes in the high-dose group varied from mild to moderate. Changes in the kidneys were characterized by eosinophilic inclusion, enlargement and anisokariosis of the epithelial lining cells, and hyperplasia of renal tubular epithelial cells. Only the changes associated with the high-dose diet were considered to be biologically significant by the investigators. Since no dose-responses can be constructed with the histological data and increases in relative kidneys weights in males did not coincide with biologically significant histological changes, this study is inadequate for use as the basis for MRL derivation.

Chronic-Duration MRL. No chronic-duration oral data in humans or animals were located for 1,3,5-trichlorobenzene; therefore, a chronic-duration oral MRL was not derived for this compound.

3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

3. HEALTH EFFECTS

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

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

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

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located regarding death in humans and/or animals after inhalation exposure to trichlorobenzenes.

3.2.1.2 Systemic Effects

There is very limited information regarding health effects in humans following exposure to trichlorobenzenes. A review of the literature indicates that an adult male who inhaled trichlorobenzene for several hours during the repair of a pump suffered massive hemoptysis, and that some trichlorobenzene production workers developed chloroacne (IPCS 1991). There is also a case report of aplastic anemia in a woman with prolonged exposure through the soaking of her husband's work clothes in trichlorobenzene (Girard et al. 1969). None of these reports provided exposure details or specified the isomer involved. Citing an unpublished source, ACGIH (2001) states that minimal eye and throat irritation could occur in some people exposed to 3–5 ppm 1,2,4-trichlorobenzene.

No information was located regarding systemic effects in animals following inhalation exposure to 1,2,3-trichlorobenzene.

3. HEALTH EFFECTS

The highest NOAEL values and all LOAEL values of 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene from each reliable study for systemic effects in each species and duration category are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2.

Respiratory Effects. Continuous exposure of male cynomolgous monkeys to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks had no significant effect on results of pulmonary function tests (static compliance, diffusion capacity, distribution of ventilation, and lung volumes) conducted in anesthetized monkeys at termination (Coate et al. 1977). Measurements of mechanical properties of the lungs conducted in unanesthetized monkeys also were not significantly affected by exposure to 1,2,4-trichlorobenzene. Histological examination of the lungs showed no treatment-related effects.

Continuous exposure of male rats to up to 100 ppm 1,2,4-trichlorobenzene vapors for up to 26 weeks did not induce significant histological alterations in the lungs (Coate et al. 1977). Similar results were reported in rats exposed to up to 200 ppm 1,2,4-trichlorobenzene vapors 6 hours/day for 15 exposures (Gage 1970) or in male rats exposed 7 hours/day, 5 days/week to up to 100 ppm 1,2,4-trichlorobenzene vapors for a total of 30 exposures (Kociba et al. 1981). Two intermediate-duration studies in rabbits exposed to up to 100 ppm 1,2,4-trichlorobenzene vapors continuously (Coate et al. 1977) or intermittently (Kociba et al. 1981) also reported no significant alterations in the lungs upon microscopic examination. Similar results were reported in dogs following intermittent intermediate-duration exposure to up to 100 ppm 1,2,4-trichlorobenzene (Kociba et al. 1981). The nasal mucosa was also examined in rats and rabbits in the Kociba et al. (1981) study.

The only information regarding 1,3,5-trichlorobenzene is from a study in male and female CD rats in which the animals were exposed 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983). Exposure to up to 130 ppm 1,3,5-trichlorobenzene vapors did not induce significant histological alterations in the lungs, trachea, or nasal passages.

Cardiovascular Effects. Continuous exposure of male monkeys, rats, or rabbits up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic alterations in the heart (Coate et al. 1977). Exposure of male rats, dogs, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors 7 hours/day, 5 days/week for a total of 30 exposures during a 40-day period did not induce significant gross or microscopic alterations in the heart or aorta (Kociba et al. 1981).

Table 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
INTERMEDIATE EXPOSURE								
Systemic								
1	Monkey (Cynomolgus)	26 wk 24 h/d	Resp	100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	100 M				
			Hemato	100 M				
			Hepatic	100 M				
			Renal	100 M				
			Dermal	100 M				
			Ocular	100 M				
			Bd Wt	100 M				
2	Rat (Sprague-Dawley)	26 wk 24 h/d	Resp	100 M			Coate et al. 1977 1,2,4-trichlorobenzene	Mild liver alterations at 4 and 13 weeks, but not 26 weeks; no quantitative data
			Cardio	100 M				
			Hemato	100 M				
			Hepatic	100 M				
			Renal	100 M				
			Dermal	100 M				
			Ocular	100 M				
			Bd Wt	100 M				

Table 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
3	Rat (Sprague-Dawley)	44 d 5 d/wk 7 h/d	Resp	100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	100 M				
			Gastro	100 M				
			Hemato	100 M				
			Musc/skel	100 M				
			Hepatic	30 M	100 M (increased relative liver weight)			
			Renal	100 M				
			Endocr	100 M				
			Ocular	100 M				
Bd Wt	100 M							

Table 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
4	Rabbit (New Zealand)	26 wk 24 h/d	Resp	100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	100 M				
			Hemato	100 M				
			Hepatic	100 M				
			Renal	100 M				
			Dermal	100 M				
			Ocular	100 M				
			Bd Wt	100 M				
5	Rabbit (New Zealand)	44 d 5 d/wk 7 h/d	Resp	100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	100 M				
			Gastro	100 M				
			Hemato	100 M				
			Musc/skel	100 M				
			Hepatic	100 M				
			Renal	100 M				
			Endocr	100 M				
			Ocular	100 M				
			Bd Wt	100 M				

Table 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference	Comments
					Less Serious (ppm)	Serious (ppm)		
Immuno/ Lymphoret								
6	Monkey (Cynomolgus)	26 wk 24 h/d		100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAEL is for spleen histopathology
7	Rat (Sprague-Dawley)	26 wk 24 h/d		100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAEL is for histopathology of the spleen
8	Rat (Sprague-Dawley)	44 d 5 d/wk 7 h/d		100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	NOAEL is for histopathology of lymphoreticular tissues
9	Rabbit (New Zealand)	26 wk 24 h/d		100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAEL is for histopathology of the spleen
10	Rabbit (New Zealand)	44 d 5 d/wk 7 h/d		100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	NOAEL is for histopathology of lymphoreticular tissues
Neurological								
11	Monkey (Cynomolgus)	26 wk 24 h/d		100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAEL is for operant behavior tests and brain and spinal cord histopathology

Table 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
12	Rat (Sprague-Dawley)	26 wk 24 h/d		100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAEL is for brain and spinal cord histopathology
13	Rat (Sprague-Dawley)	44 d 5 d/wk 7 h/d		100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	NOAEL is for histopathology of central and peripheral nervous tissues
14	Rabbit (New Zealand)	26 wk 24 h/d		100 M			Coate et al. 1977 1,2,4-trichlorobenzene	NOAEL is for histopathology of the brain and spinal cord
15	Rabbit (New Zealand)	44 d 5 d/wk 7 h/d		100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	NOAEL is for histopathology of central and peripheral nervous tissues
Reproductive								
16	Rat (Sprague-Dawley)	44 d 5 d/wk 7 h/d		100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	NOAEL is for histopathology of reproductive organs
17	Rabbit (New Zealand)	44 d 5 d/wk 7 h/d		100 M			Kociba et al. 1981 1,2,4-trichlorobenzene	No histopathological effects in reproductive organs

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

Bd Wt = body weight; (Cardio = cardiovascular; d = day(s); Endocr = endocrine; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s))

Figure 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation
Intermediate (15-364 days)

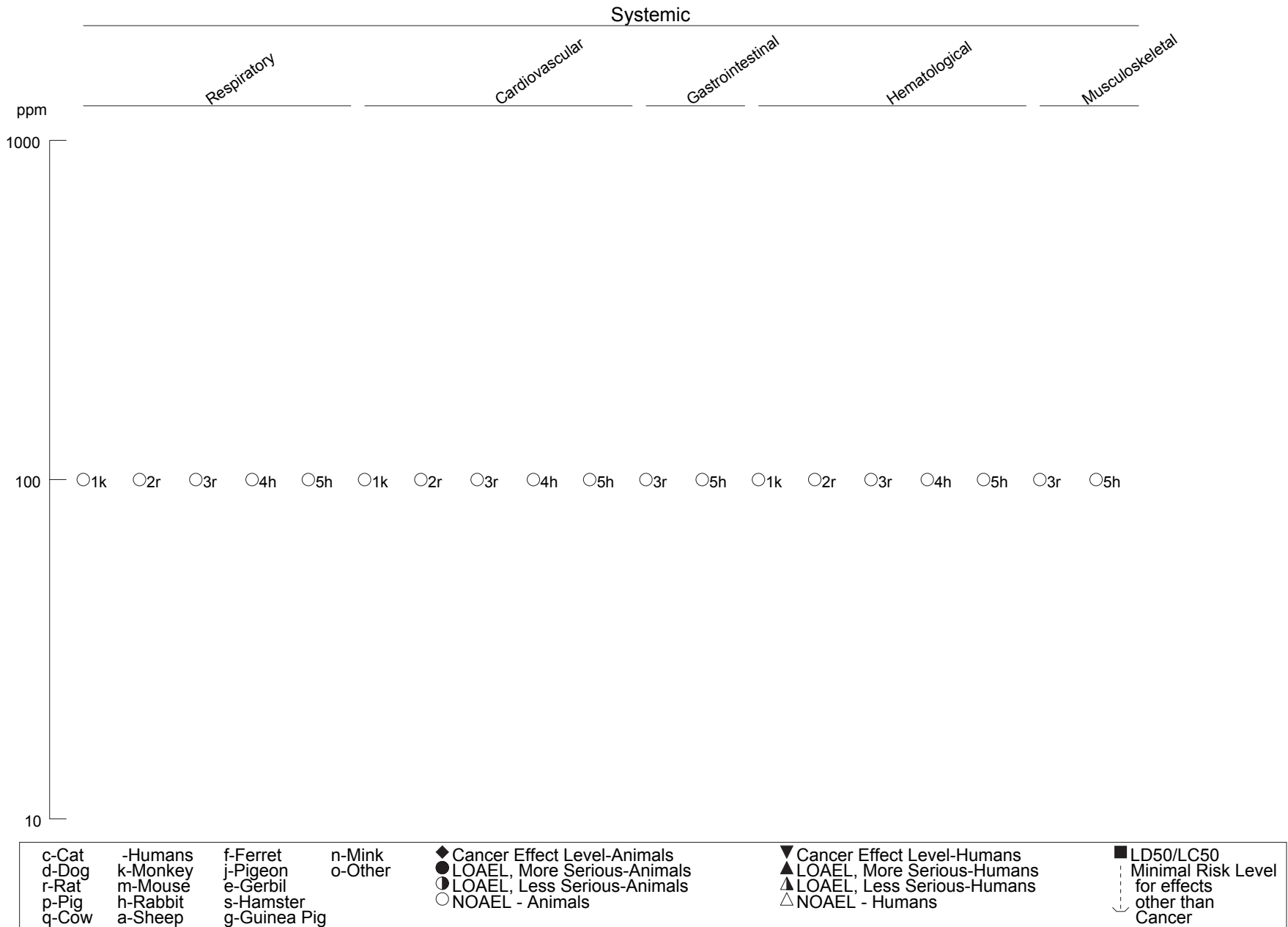


Figure 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation (Continued)
Intermediate (15-364 days)

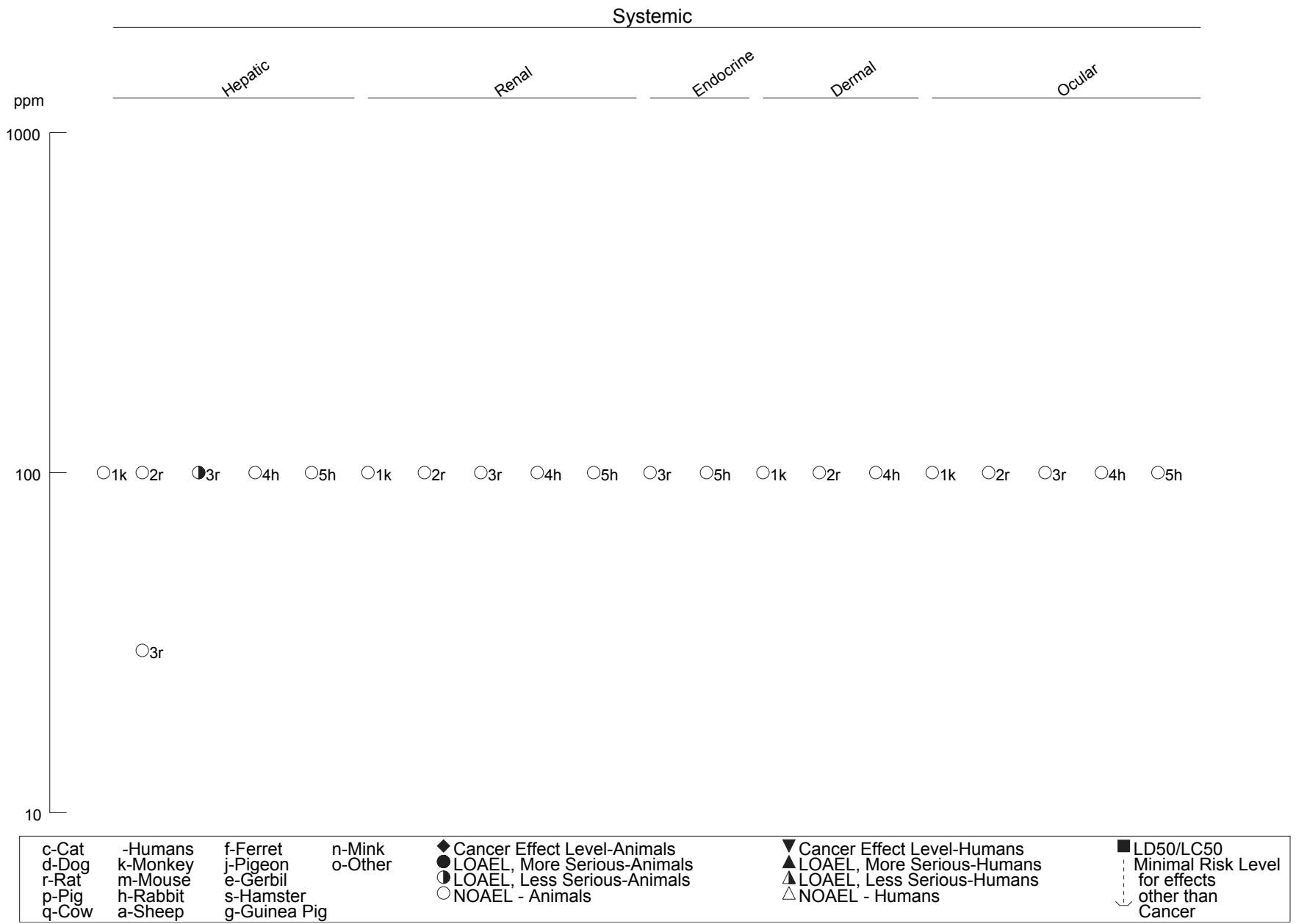


Figure 3-1 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Inhalation (Continued)

Intermediate (15-364 days)

Systemic

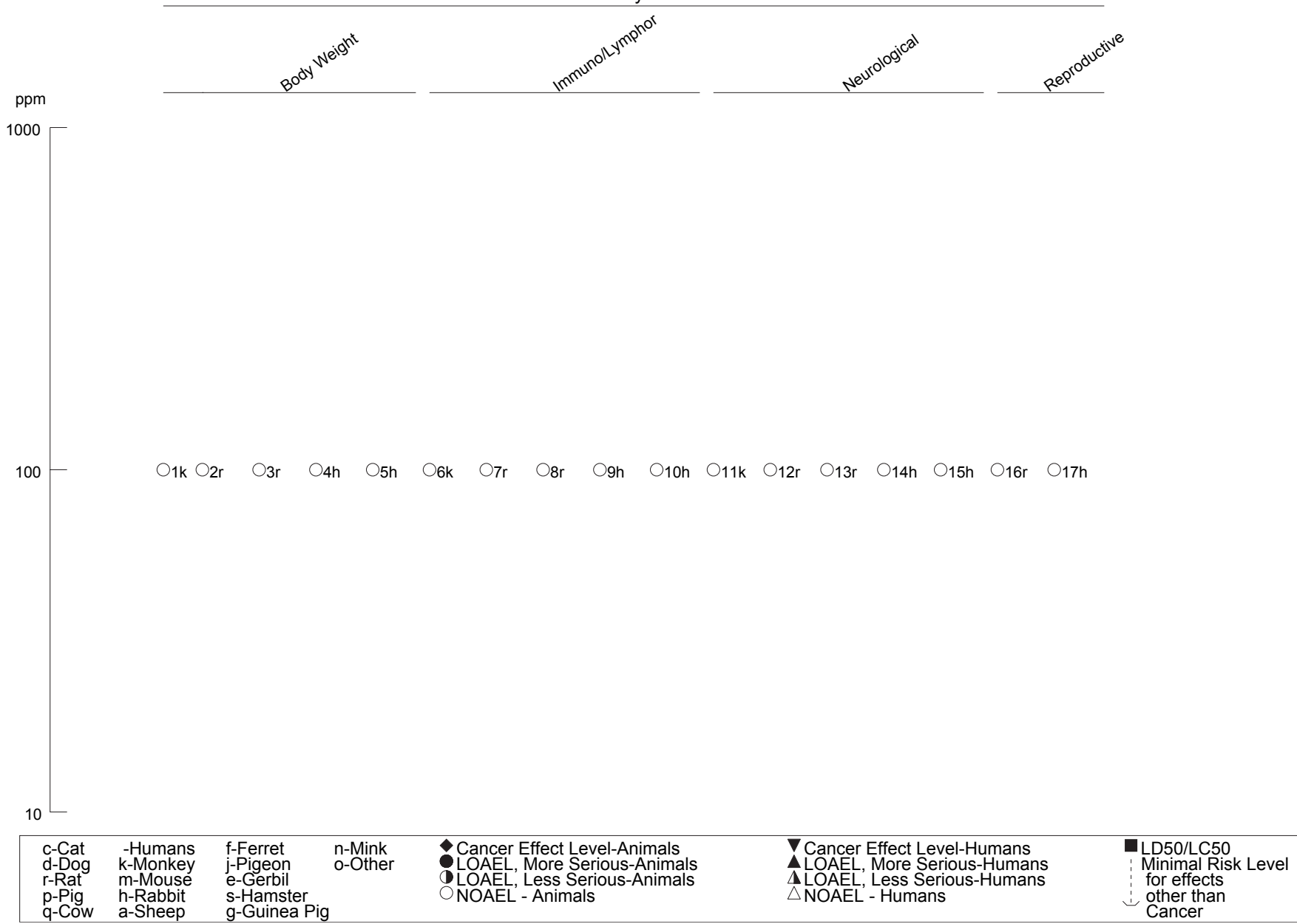


Table 3-2 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Inhalation

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	1 hr	Bd Wt			1209	(44-60% less weight than controls 14 days after exposure)	Jorgenson et al. 1976 1,3,5-Trichlorobenzene
INTERMEDIATE EXPOSURE								
Systemic								
2	Rat (CD)	13 wk 5 d/wk 6 h/d	Resp	130				Sasmore et al. 1983 1,3,5-Trichlorobenzene
			Cardio	130				
			Gastro	130				
			Hemato	130				
			Hepatic	130				
			Renal	130				
			Endocr	130				
			Ocular	130				
			Bd Wt	130				
Immuno/ Lymphoret								
3	Rat (CD)	13 wk 5 d/wk 6 h/d		130				Sasmore et al. 1983 1,3,5-Trichlorobenzene
Neurological								
4	Rat (CD)	13 wk 5 d/wk 6 h/d		130				Sasmore et al. 1983 1,3,5-Trichlorobenzene

Table 3-2 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
Reproductive								
5	Rat (CD)	13 wk 5 d/wk 6 h/d		130			Sasmore et al. 1983 1,3,5-Trichlorobenzene	NOAEL is for histopathology of reproductive organs

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

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 3-2 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Inhalation
Acute (≤14 days)

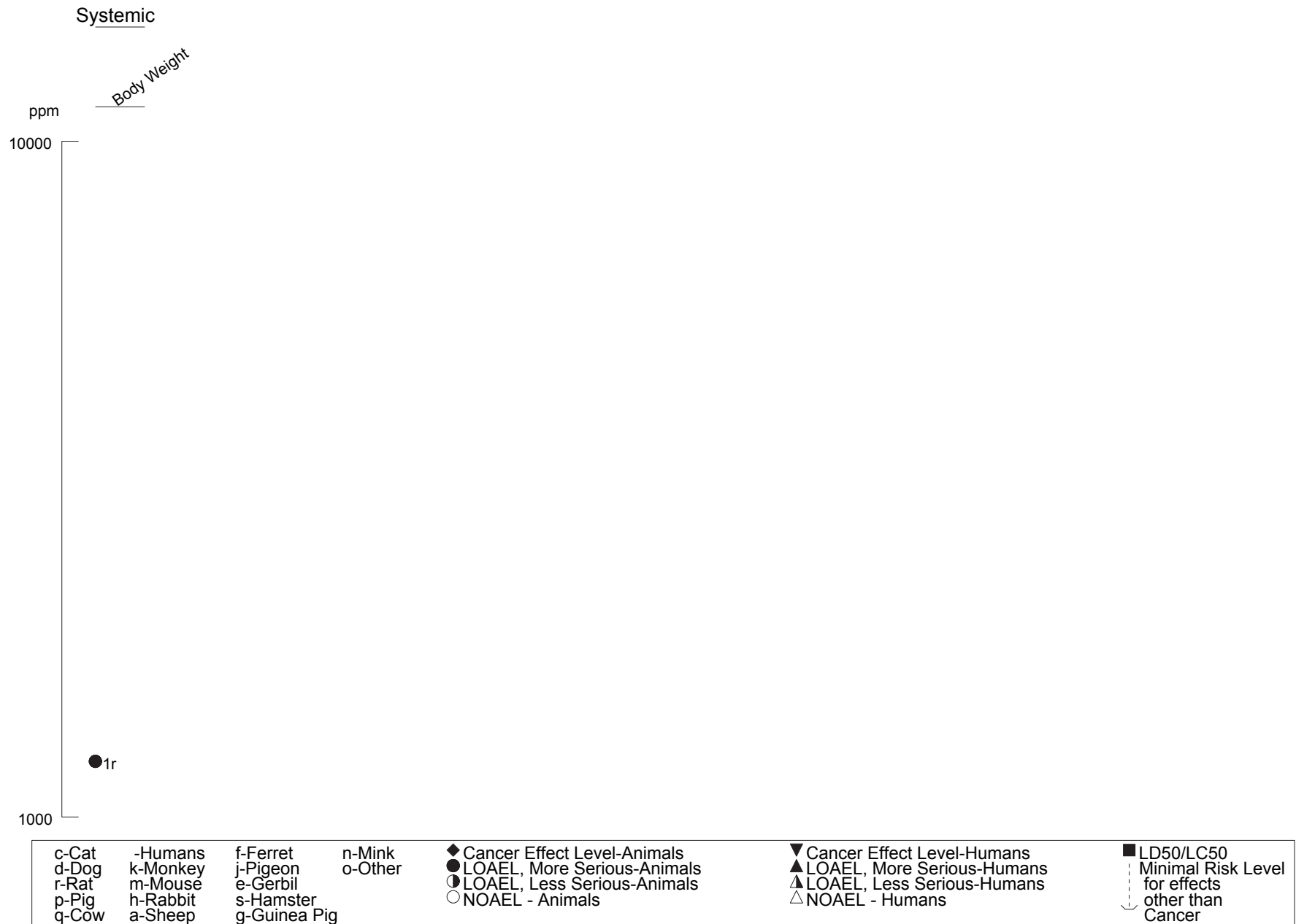
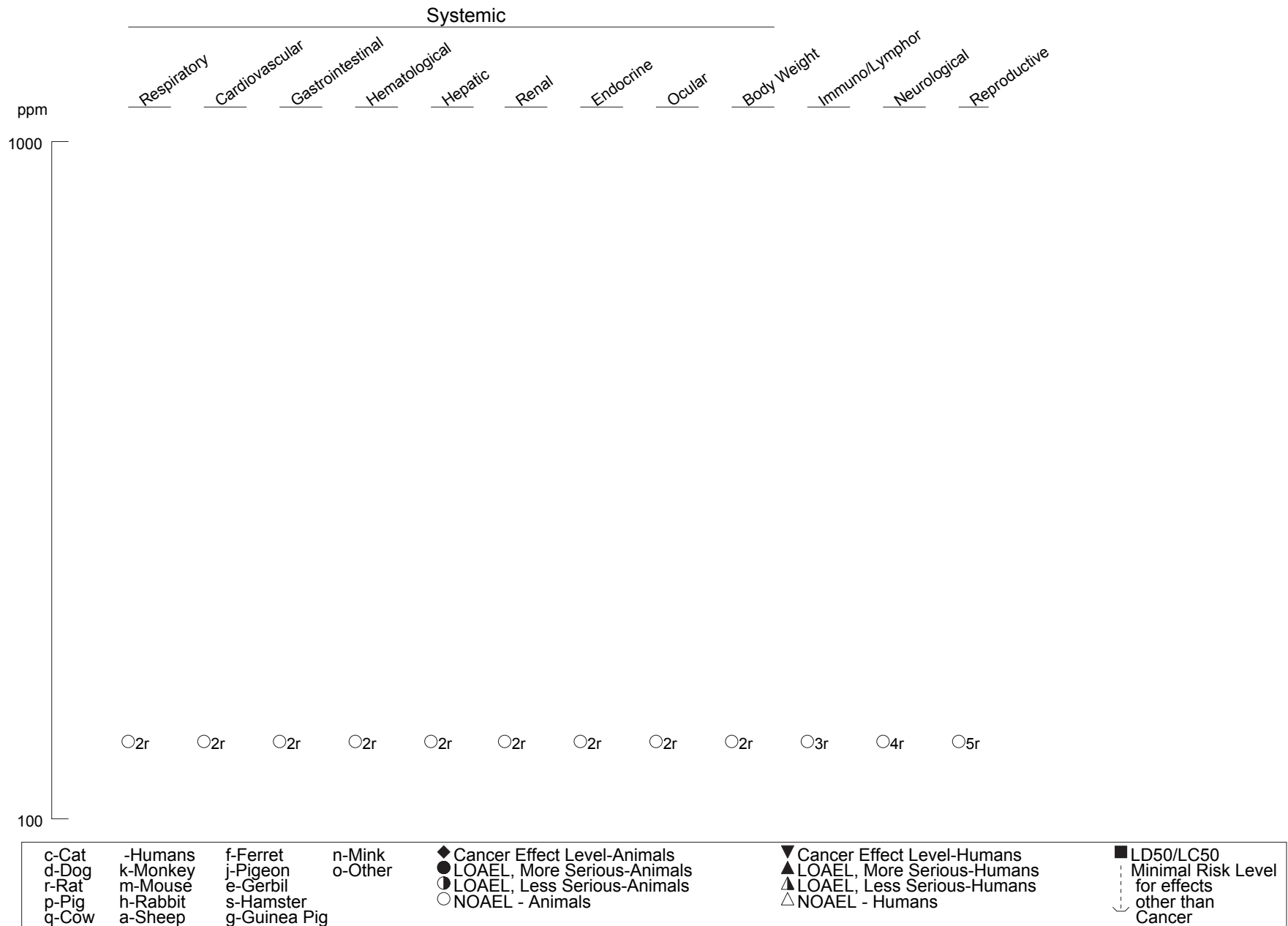


Figure 3-2 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Inhalation (Continued)
Intermediate (15-364 days)



3. HEALTH EFFECTS

Exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks did not induce histological changes in the heart (Sasmore et al. 1983).

Gastrointestinal Effects. Exposure of male rats, dogs, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors 7 hours/day, 5 days/week for a total of 30 exposures during a 40-day period did not induce significant gross or microscopic alterations in the gastrointestinal tract (Kociba et al. 1981). Similar results were reported for the gastrointestinal tract of rats exposed to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983).

Hematological Effects. Complete blood counts performed on male monkeys, rats, and rabbits exposed continuously to up to 100 ppm 1,2,4-trichlorobenzene vapors for up to 26 weeks did not show any significant exposure-related differences from controls (Coate et al. 1977). Kociba et al. (1981) reported no significant alterations in total red blood cells, total differential leukocytes, packed cell volume or hemoglobin concentration in blood samples from male rats, rabbits, and dogs following 30 intermittent exposures to up to 100 ppm 1,2,4-trichlorobenzene vapors.

Exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene 6 hours/day, 5 days/week for 13 weeks did not significantly alter blood cell counts and mean corpuscular values, differential counts, or platelet counts (Sasmore et al. 1983). Methemoglobin was slightly higher at 13 weeks than at 4 weeks, but values did not reach significant levels (data not shown).

Musculoskeletal Effects. No significant alterations were reported in skeletal muscle from male rats, rabbits, and dogs following 30 intermittent exposures to up to 100 ppm 1,2,4-trichlorobenzene vapors (Kociba et al. 1981).

In the 13-week inhalation study with 1,3,5-trichlorobenzene (Sasmore et al. 1983), there is no explicit indication that musculoskeletal tissues were examined, although the investigators stated that 34 specific organs and tissues from the control and the high-exposure groups (130 ppm) were examined microscopically. Therefore, it is reasonable to assume that evaluations were conducted and that no alterations were observed.

Hepatic Effects. Continuous exposure of male monkeys or rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic alterations in the liver (Coate et al. 1977). However, exposure-related liver changes were described in rats (only qualitative description

3. HEALTH EFFECTS

provided). The changes were characterized as mild and were seen in all exposed groups (25, 50, 100 ppm) usually after 4 and 13 weeks but not at 26 weeks. Hepatocytomegaly occurred in all exposed groups but seemed more noticeable in the mid- and high-exposure groups. There was also a slight increase in the degree of vacuolization of hepatocytes in exposed rats that did not appear dose-related. Hepatocytomegaly was present in all exposed groups at 4 weeks and in the mid- and high-exposure groups at 13 weeks. Exposed rats also showed a slight increase in incidence of granuloma at 4 weeks, which did not appear to be dose-related. No histological alterations were reported in the liver from rats following 15 exposures to 200 ppm 1,2,4-trichlorobenzene each lasting 6 hours (Gage 1970).

Changes in liver weight were reported in rats, dogs, and rabbits exposed to 100 ppm 1,2,4-trichlorobenzene vapors 7 hours/day, 5 days/week for a total of 30 exposures during a 44-day period (Kociba et al. 1981). These changes were not accompanied by histological alterations or alterations in clinical chemistry tests for liver function. In rats, relative liver weight increased 11% relative to controls. Urinalyses conducted after 15 and 30 days of exposure showed statistically significant increased coproporphyrins and uroporphyrins in both the low- (30 ppm) and high-dose rats (100 ppm), which the investigators attributed to the ability of 1,2,4-trichlorobenzene to induce hepatic microsomal enzymes rather than to induce destruction of heme-containing cytochromes or inhibition of heme synthesis. In dogs, both absolute and relative liver weights were increased (27–30%). In rabbits, relative liver weight was decreased 16% relative to controls. Urinary porphyrins levels were not examined in dogs or rabbits.

Exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks did not significantly affect liver weight or the gross or microscopic appearance of the liver (Sasmore et al. 1983). Urinary porphyrin levels were elevated in males at 13 weeks, but large variability rendered the differences with controls nonsignificant.

Renal Effects. Continuous exposure of male monkeys or rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic alterations in the kidneys (Coate et al. 1977). Male rats exposed in a similar manner showed kidney changes characterized as mild and present in all exposed groups usually after 4 and 13 weeks but not at 26 weeks of exposure (only a qualitative description was provided). Exposed male rats showed hyaline degeneration in the inner zone of the cortex, which appeared more severe at 4 weeks but was not dose-related; severity appeared increased at 13 weeks in high-dose rats. No histological alterations were reported in the kidneys from rats following 15 exposures to 200 ppm 1,2,4-trichlorobenzene each lasting 6 hours (Gage 1970), or in the

3. HEALTH EFFECTS

kidneys from rats, rabbits, and dogs exposed to up to 100 ppm 1,2,4-trichlorobenzene vapors 7 hours/day, 5 days/week for 30 exposures during a 44-day period (Kociba et al. 1981).

Exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks did not result in significant gross or microscopic alterations in the kidneys (Sasmore et al. 1983).

Endocrine Effects. Fifteen 6-hour exposures to up to 200 ppm 1,2,4-trichlorobenzene vapors did not induce significant gross or histological alterations in the adrenal glands from rats (Gage 1970). Exposure of rats, dogs, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors 7 hours/day, 5 days/week for a total of 30 exposures did not induce significant gross or microscopic alterations in the pituitary gland, adrenal gland, thyroid, or parathyroid (Kociba et al. 1981).

In the 13-week study of rats exposed intermittently to up to 130 ppm 1,3,5-trichlorobenzene vapors, the investigators stated that 34 organs were examined in the control and high-dose groups but did not specify the organs (Sasmore et al. 1983). However, there is mention that hemosiderosis was noted in the thyroid gland, which, by the distribution and nature in the different groups, appeared unrelated to the treatment. It seems reasonable to assume that other endocrine glands were also examined and that no alterations were observed.

Dermal Effects. Continuous exposure of male monkeys, rats, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic alterations in a section of abdominal skin that was examined (Coate et al. 1977).

No relevant data were located regarding 1,3,5-trichlorobenzene.

Ocular Effects. Gage (1970) reported that lacrimation occurred in rats initially during the 6-hour exposures to 70 ppm 1,2,4-trichlorobenzene but not during exposures to 20 ppm 1,2,4-trichlorobenzene. Continuous exposure of male monkeys, rats, or rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic alterations in the eyes (Coate et al. 1977). The eyes from rats, dogs, and rabbits were also examined in the intermediate-duration study by Kociba et al. (1981). In that study, exposure to up to 100 ppm 1,2,4-trichlorobenzene vapors did not induce alterations in the microscopic morphology of the eye.

3. HEALTH EFFECTS

Body Weight Effects. Continuous exposure of male monkeys, rats, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks (Coate et al. 1977) or intermittent exposure of rats, dogs, and rabbits to up to 100 ppm for 44 days (Kociba et al. 1981) did not significantly alter body weight. Gage (1970) reported that rats exposed to 70 ppm 1,2,4-trichlorobenzene 6 hours/day for 15 exposures showed retarded weight gain, but no data were presented.

Exposure of rats to 1,209 ppm 1,3,5-trichlorobenzene vapors for 60 minutes resulted in 44 and 60% less body weight gain in males and females, respectively, 14 days after exposure (Jorgenson et al. 1976). Body weight was not affected in rats exposed intermittently to up to 130 ppm 1,3,5-trichlorobenzene vapors for 13 weeks (Sasmore et al. 1983).

Metabolic Effects. Intermittent exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene vapors for 13 weeks did not significantly affect serum electrolyte levels or electrolyte balance (Sasmore et al. 1983).

No relevant data were located regarding 1,2,4-trichlorobenzene.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to trichlorobenzenes.

Continuous exposure of monkeys, rats, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic changes in the spleen of the animals (Coate et al. 1977). Fifteen intermittent exposures (6 hours/day) of rats to up to 200 ppm 1,2,4-trichlorobenzene vapors also did not result in significant histological alterations in the spleen (Gage 1970). Similar experiments in rats, rabbits, and dogs exposed 7 hours/day, 5 days/week to up to 100 ppm 1,2,4-trichlorobenzene vapors for a total of 30 exposures during a 44-day period did not result in significant gross or microscopic alterations in the spleen, thymus, or lymph nodes (Kociba et al. 1981).

No histological alterations were observed in lymphoreticular tissues from rats exposed to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983).

No relevant data were located regarding 1,2,3-trichlorobenzene.

3. HEALTH EFFECTS

NOAELs for lymphoreticular effects of 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene are presented in Tables 3-1 and 3-2 and are plotted in Figures 3-1 and 3-2.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to trichlorobenzenes.

Lethargy was reported in rats during 6-hour exposures to 70 ppm 1,2,4-trichlorobenzene vapors (Gage 1970). No such effect was observed during exposures to 20 ppm.

Continuous exposure of monkeys, rats, or rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic changes in the brain and spinal cord (Coate et al. 1977). Operant behavior tests conducted in the monkeys throughout the study showed no exposure-related alterations. Similar lack of gross or histological alterations were reported in the brain, spinal cord, and peripheral nerves from rats, dogs, and rabbits exposed intermittently to up to 100 ppm 1,2,4-trichlorobenzene vapors during a 44-day period (Kociba et al. 1981).

No histological alterations were observed in the brain and spinal cord from rats exposed to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983).

No relevant data were located regarding 1,2,3-trichlorobenzene.

NOAELs and LOAELs for neurological effects are presented in Tables 3-1 and 3-2 and are plotted in Figures 3-1 and 3-2.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to trichlorobenzenes.

No significant gross or histological alterations were reported in the reproductive organs from male rats, dogs, and rabbits exposed intermittently to up to 100 ppm 1,2,4-trichlorobenzene vapors for 44 days (Kociba et al. 1981). It should be noted, however, that absolute and relative testes weights were significantly increased (30 and 43%, respectively) in rabbits exposed to 100 ppm (but not 30 ppm). The

3. HEALTH EFFECTS

investigators considered this change unrelated to the test material since, as indicated above, microscopic examination did not reveal any significant histological changes.

No histological alterations were observed in the reproductive organs from male or female rats exposed to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983).

No relevant data were located regarding 1,2,3-trichlorobenzene.

NOAELs for reproductive effects are presented in Table 3-1 and are plotted in Figure 3-1.

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

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to trichlorobenzenes.

Information regarding acute lethality is available for the three trichlorobenzene isomers. An LD₅₀ of 756 mg/kg was reported for 1,2,4-trichlorobenzene in CFE rats (Brown et al. 1969). In the same study, the investigators determined an oral LD₅₀ of 766 mg/kg for 1,2,4-trichlorobenzene in C57BL/6N mice. In both species, lower doses caused depression of activity, while lethal doses induced extensor convulsions. Another study reported an LD₅₀ of 880 mg/kg for 1,2,4-trichlorobenzene in Sprague-Dawley rats (Côté et al. 1988). In a developmental study, six out of six pregnant Sprague-Dawley rats died after 3 days of dosing with 1,200 mg/kg 1,2,4-trichlorobenzene (Kitchin and Ebron 1983).

Without providing further details, Côté et al. (1988) reported that the oral LD₅₀ for 1,2,3-trichlorobenzene in Sprague-Dawley rats was 1,830 mg/kg. In a brief report in which groups of two rats per group were administered 1,000 or 2,000 mg/kg 1,2,3-trichlorobenzene by gavage in corn oil, one rat in the high-dose

3. HEALTH EFFECTS

group died within 2 days of dosing (Dow Chemical 1956). The investigators stated that slight pathology of the liver and spleen occurred, but no details were provided.

An oral LD₅₀ of 2,100 mg/kg was reported for 1,3,5-trichlorobenzene in Sprague-Dawley rats (Côté et al. 1988). In another study, Jorgenson et al. (1976) reported LD₅₀ values of 1,800 and 2,800 mg/kg for 1,3,5-trichlorobenzene in male and female Sprague-Dawley rats, respectively. All deaths except one occurred between 21 and 96 hours after dosing. Clinical signs observed included rough hair coat, passive tremors, depression, and inactivity leading to prostration, persistent tremor, coma, and death; necropsy revealed no gross abnormalities. The corresponding oral LD₅₀ values for 1,3,5-trichlorobenzene in male and female ICR mice were 3,350 and 3,402 mg/kg, respectively (Jorgenson et al. 1976). Clinical signs observed included rough hair coat, passive tremors, depression, inactivity, prostration, persistent tremors, coma, and death. Deaths occurred between 22 and 288 hours after dosing; necropsy revealed no gross abnormalities. Increased mortality rate was reported in male rats dosed with 66.5 mg/kg/day 1,2,4-trichlorobenzene for 104 weeks (Moore 1994a). Similar results were reported in male and female mice dosed with 519.9 and 572.6 mg/kg/day 1,2,4-trichlorobenzene, respectively, for 104 weeks (Moore 1994b).

The limited data available suggest that 1,2,4-trichlorobenzene has a stronger acute toxicity than the other two isomers, and that rats may be more susceptible than mice.

Lethal doses and LD₅₀ values are presented in Tables 3-3, 3-4, and 3-5 and plotted in Figures 3-3, 3-4, and 3-5.

3.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans after oral exposure to trichlorobenzenes.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 3-3, 3-4, and 3-5 and plotted in Figure 3-3, 3-4, and 3-5.

Respiratory Effects. No gross or microscopic alterations were observed in the lungs, bronchi, or trachea from rats administered up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3- or 1,3,5-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22 (Black et al. 1988). In intermediate-duration

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (G)				756 (LD50)	Brown et al. 1969 1,2,4-trichlorobenzene	
2	Rat (Sprague-Dawley)	once (G)				880 (LD50)	Cote et al. 1988 1,2,4-trichlorobenzene	
3	Rat (NS)	once (G)				2250 (lowest lethal dose)	E.I. Dupont 1971 1,2,4-trichlorobenzene	
4	Rat (Sprague-Dawley)	Gd 9-13 1 x/d (GO)				1200 F (6/6 died after 3 days of dosing)	Kitchin and Ebron 1983 1,2,4-trichlorobenzene	
5	Mouse (C57BL/6N)	once (G)				766 (LD50)	Brown et al. 1969 1,2,4-trichlorobenzene	

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency/ (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic								
6	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)	Resp	300 F			Black et al. 1988 1,2,4-trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	300 F				
			Gastro	300 F				
			Hemato	300 F				
			Musc/skel	300 F				
			Hepatic	150 F	300 F (11% increase in relative liver weight)			
			Renal	300 F				
			Dermal	300 F				
			Ocular	300 F				
Metab	300 F							
7	Rat (albino)	14 d 1 x/d (GO)	Hemato	40 M			Carlson and Tardiff 1976 1,2,4-trichlorobenzene	
			Hepatic		10 M (15% increase in relative liver weight; increased phase I and phase II enzyme activity)			
8	Rat (NS)	3 d 1 x/d (GO)	Bd Wt		450	(4% weight loss in 3 days)	E.I. Dupont 1971 1,2,4-trichlorobenzene	

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
9	Rat (Sprague-Dawley)	Gd 9-13 1 x/d (GO)	Hepatic	36 F	120 F (increased phase I and phase II metabolic enzyme activity)		Kitchin and Ebron 1983 1,2,4-trichlorobenzene	Moderate hepatocellular hypertrophy at 360 mg/kg/day
			Bd Wt	120 F		360 F (17 grams lost, controls gained 37 grams)		
10	Rat (albino)	10 d 1 x/d (G)	Hepatic			500 M (intense necrosis and fatty change)	Rimington and Ziegler 1963 1,2,4-trichlorobenzene	
			Bd Wt			500 M (weight loss)		
11	Mouse (CD-1)	Gd 8-12 1 x/d (G)	Bd Wt	130 F			Chernoff and Kavlock 1983 1,2,4-trichlorobenzene	NOAEL is for maternal weight change during treatment
Immuno/ Lymphoret								
12	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		300 F			Black et al. 1988 1,2,4-trichlorobenzene	NOAEL is for histopathology of the thymus and spleen
Neurological								
13	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		300 F			Black et al. 1988 1,2,4-trichlorobenzene	NOAEL is for histopathology of the brain and peripheral nerve

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
Reproductive							
14	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		300 F		Black et al. 1988 1,2,4-trichlorobenzene	NOAEL is for histopathology of the ovaries and uterus
Developmental							
15	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		300		Black et al. 1988 1,2,4-trichlorobenzene	Lesions in pup's lenses occurred at 75 mg/kg/day; incidences not reported
16	Rat (Sprague- Dawley)	Gd 9-13 1 x/d (GO)			360 F (retarded fetal development)	Kitchin and Ebron 1983 1,2,4-trichlorobenzene	
17	Mouse (CD-1)	Gd 8-12 1 x/d (G)		130		Chernoff and Kavlock 1983 1,2,4-trichlorobenzene	NOAEL is for neonatal weight and viability.
18	Mouse (CD-1)	Gd 8-12 1 x/d (GO)		130		Gray and Kavlock 1984 1,2,4-trichlorobenzene	NOAEL is for viability of F1 and reproductive performance of F1
19	Mouse (CD-1)	Gd 8-12 1 x/d (GO)		130		Gray et al. 1986 1,2,4-trichlorobenzene	NOAEL is for reactive locomotor activity of pups exposed in utero

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
INTERMEDIATE EXPOSURE								
Systemic								
20	Rat (albino)	90 d 1 x/d (GO)	Hemato	40 M			Carlson and Tardiff 1976 1,2,4-trichlorobenzene	No liver histopathology
			Hepatic	20 M	40 M (14% increase in relative liver weight after 30-day recovery period; increased phase I metabolic enzymes)			
			Bd Wt	40 M				

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
21	Rat (Fischer- 344)	14 wk ad lib (F)	Resp	150.6 F			CMA 1989 1,2,4-trichlorobenzene	NOAELs are for histopathology of tissues and organs.
			Cardio	150.6 F				
			Gastro	150.6 F				
			Hemato	150.6 F				
			Musc/skel	150.6 F				
			Hepatic	14.6 ^b M	45.6 M (increased liver weight, hepatocyte hypertrophy)			
			Renal	45.6 M	133.7 M (increased kidney weight; dilated tubules, granular casts; interstitial nephritis; elevated BUN)			
			Endocr	150.6 F				
			Ocular	150.6 F				
			Bd Wt	150.6 F				
Metab	150.6 F							

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
22	Rat (Sprague-Dawley)	13 wk ad lib (F)	Resp	101 F			Cote et al. 1988 1,2,4-trichlorobenzene	NOAELs are for organ histopathology
			Cardio	101 F				
			Gastro	101 F				
			Hemato	101 F				
			Musc/skel	101 F				
			Hepatic	7.8 M	82 M (13-20% increased absolute and relative liver weight)			
			Renal	7.8 M	82 M (31-36% increase absolute and relative kidney weight)			
			Dermal	101 F				
			Ocular	101 F				
			Bd Wt	101 F				
	Metab	101 F						
23	Rat (albino)	15 d 1 x/d (G)	Hepatic			730 M (intense necrosis and fatty change)	Rimington and Ziegler 1963 1,2,4-trichlorobenzene	
			Bd Wt			730 M (weight loss)		

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
24	Mouse (B6C3F1)	13 wk ad lib (F)	Resp	1345 F			Hiles 1989 1,2,4-trichlorobenzene NOAELs are for histopathology of organs and tissues
			Cardio	1345 F			
			Gastro	1345 F			
			Hemato	1345 F			
			Musc/skel	1345 F			
			Hepatic	67 M	850 M (hepatocyte hypertrophy, atrophy, vacuolar degeneration, necrosis; higher ALT and SDH activities)		
			Renal	1345 F			
			Endocr	1345 F			
			Ocular	1345 F			
		Metab	1345 F				
Immuno/ Lymphoret							
25	Rat (Fischer- 344)	14 wk ad lib (F)		150.6 F			CMA 1989 1,2,4-trichlorobenzene NOAEL is for histopathology of lymphoreticular tissues
26	Rat (Sprague-Dawley)	13 wk ad lib (F)		101 F			Cote et al. 1988 1,2,4-trichlorobenzene NOAEL is for histopathology of lymphoreticular organs

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
27	Mouse (B6C3F1)	13 wk ad lib (F)		1345 F		Hiles 1989 1,2,4-trichlorobenzene	NOAEL is for histopathology of lymphoreticular organs
Neurological							
28	Rat (Fischer- 344)	14 wk ad lib (F)		150.6 F		CMA 1989 1,2,4-trichlorobenzene	NOAEL is for histopathology of central and peripheral nervous tissues
29	Rat (Sprague-Dawley)	13 wk ad lib (F)		101 F		Cote et al. 1988 1,2,4-trichlorobenzene	NOAEL is for histopathology of central and peripheral nervous tissue
30	Mouse (B6C3F1)	13 wk ad lib (F)		1345 F		Hiles 1989 1,2,4-trichlorobenzene	NOAEL is for histopathology of brain and spinal cord
Reproductive							
31	Rat (Fischer- 344)	14 wk ad lib (F)		133.7 M 150.6 F		CMA 1989 1,2,4-trichlorobenzene	NOAEL is for histopathology of reproductive organs
32	Rat (Sprague-Dawley)	13 wk ad lib (F)		82 M 101 F		Cote et al. 1988 1,2,4-trichlorobenzene	NOAEL is for histopathology of reproductive organs

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
33	Rat (Sprague- Dawley)	90 d ad lib (W)		33 M		Robinson et al. 1981 1,2,4-trichlorobenzene	NOAEL is for fertility of F0 and F1 generation
				53.6 F			
34	Mouse (B6C3F1)	13 wk ad lib (F)		1222 M		Hiles 1989 1,2,4-trichlorobenzene	NOAEL is for histopathology of reproductive organs
				1345 F			
Developmental							
35	Rat (Sprague- Dawley)	90 d ad lib (W)		53.6 F		Robinson et al. 1981 1,2,4-trichlorobenzene	NOAEL is for standard neonatal indices, locomotor activity, clinical chemistry in offspring
CHRONIC EXPOSURE							
Death							
36	Rat (Fischer- 344)	104 wk ad lib (F)			66.5 M (decreased survival)	Moore 1994a 1,2,4-trichlorobenzene	
37	Mouse (B6C3F1)	104 wk ad lib (F)			519.9 M (decreased survival)	Moore 1994b 1,2,4-trichlorobenzene	
					572.6 F (decreased survival)		

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic								
38	Rat (Fischer-344)	104 wk ad lib (F)	Resp	81.4 F			Moore 1994a 1,2,4-trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	81.4 F				
			Gastro	81.4 F				
			Hemato	81.4 F				
			Musc/skel	81.4 F				
			Hepatic	19.4 M ^c	66.5 M (increased liver weight; hepatocellular hypertrophy)			
			Renal	19.4 M	66.5 M (renal transitional cell hyperplasia)			
			Endocr	81.4 F				
			Dermal	81.4 F				
			Ocular	81.4 F				
			Bd Wt	81.4 F				

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
39	Mouse (B6C3F1)	104 wk ad lib (F)	Resp	572.6 F			Moore 1994b 1,2,4-trichlorobenzene NOAELs are for tissues and organs histopathology
			Cardio	572.6 F			
			Gastro	572.6 F			
			Hemato	572.6 F			
			Musc/skel	572.6 F			
			Hepatic	21 M	100.6 M (centrilobular hepatocytomegaly)		
					26.3 F (increased absolute and relative liver weight)		
			Renal	572.6 F			
			Endocr	572.6 F			
			Dermal	572.6 F			
Ocular	572.6 F						
Bd Wt	100.6 M	519.9 M (16% decreased final body weight)					
Immuno/ Lymphoret							
40	Rat (Fischer- 344)	104 wk ad lib (F)		81.4 F			Moore 1994a 1,2,4-trichlorobenzene NOAEL is for histopathology of lymphoreticular tissues

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
41	Mouse (B6C3F1)	104 wk ad lib (F)		572.6 F		Moore 1994b 1,2,4-trichlorobenzene	NOAEL is for histopathology of lymphoreticular tissues
Neurological							
42	Rat (Fischer- 344)	104 wk ad lib (F)		81.4 F		Moore 1994a 1,2,4-trichlorobenzene	NOAEL is for nervous system histopathology
43	Mouse (B6C3F1)	104 wk ad lib (F)		572.6 F		Moore 1994b 1,2,4-trichlorobenzene	NOAEL is for histopathology of peripheral and central nervous tissues
Reproductive							
44	Rat (Fischer- 344)	104 wk ad lib (F)		66.5 M 81.4 F		Moore 1994a 1,2,4-trichlorobenzene	NOAEL is for histopathology of reproductive organs
45	Mouse (B6C3F1)	104 wk ad lib (F)		519.9 M 572.6 F		Moore 1994b 1,2,4-trichlorobenzene	NOAELs are for histopathology of reproductive organs

Table 3-3 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Cancer								
46	Mouse (B6C3F1)	104 wk ad lib (F)				100.6 M (CEL: hepatocellular carcinoma)	Moore 1994b 1,2,4-trichlorobenzene	
						127 F (CEL: hepatocellular carcinoma)		

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

b Used to derive an intermediate-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene; the MRL was derived by dividing the BMDL10 by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene; the MRL was derived by dividing the BMDL10 by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (W) = drinking water; wk = week(s); x = time(s)

Table 3-4 Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (F)				1830 (LD50)	Cote et al. 1988 1,2,3-Trichlorobenzene	
2	Rat (NS)	once (GO)				2000 (1 out of 2 rats died within two days of dosing)	Dow Chemical 1956 1,2,3-Trichlorobenzene	
Systemic								
3	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)	Resp	600 F			Black et al. 1988 1,2,3-Trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	600 F				
			Gastro	600 F				
			Hemato	600 F				
			Musc/skel	600 F				
			Hepatic	150 F	300 F (14% increase in relative liver weight)			
			Dermal	600 F				
			Ocular	600 F				
			Metab	600 F				
4	Rat (albino)	7 d 1 x/d (G)	Bd Wt			780 M (weight loss)	Rimington and Ziegler 1963 1,2,3-Trichlorobenzene	

Table 3-4 Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Immuno/ Lymphoret								
5	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		600 F			Black et al. 1988 1,2,3-Trichlorobenzene	NOAEL is for histopathology of spleen and thymus
Neurological								
6	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		600 F			Black et al. 1988 1,2,3-Trichlorobenzene	NOAEL is for histopathology of brain and peripheral nerve
Reproductive								
7	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		600 F			Black et al. 1988 1,2,3-Trichlorobenzene	NOAEL is for histopathology of reproductive organs
Developmental								
8	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		600			Black et al. 1988 1,2,3-Trichlorobenzene	NOAELs are for histopathology of organs and tissues from pups

Table 3-4 Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
INTERMEDIATE EXPOSURE								
Systemic								
9	Rat (Sprague-Dawley)	13 wk ad lib (F)	Resp	113 F			Cote et al. 1988 1,2,3-Trichlorobenzene	NOAELs are for organ histopathology
			Cardio	113 F				
			Gastro	113 F				
			Hemato	113 F				
			Musc/skel	113 F				
			Hepatic	7.6 M	78 M (14% increase in relative liver weight)			
			Renal	7.6 M	78 M (21% increase in relative kidney weight)			
			Dermal	113 F				
			Ocular	113 F				
			Bd Wt	7.6 M	78 M (10.2% reduced body weight gain)			
			Metab	113 F				
Immuno/ Lymphoret								
10	Rat (Sprague-Dawley)	13 wk ad lib (F)		113 F			Cote et al. 1988 1,2,3-Trichlorobenzene	NOAEL is for histopathology of lymphoreticular tissues
Neurological								
11	Rat (Sprague-Dawley)	13 wk ad lib (F)		113 F			Cote et al. 1988 1,2,3-Trichlorobenzene	NOAEL is for histopathology of central and peripheral nerve tissues

Table 3-4 Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Reproductive								
12	Rat (Sprague-Dawley)	13 wk ad lib (F)		78 M 113 F			Cote et al. 1988 1,2,3-Trichlorobenzene	NOAEL is for histopathology of reproductive organs

^a The number corresponds to entries in Figure 3-4.

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-4 Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral
Acute (≤14 days)

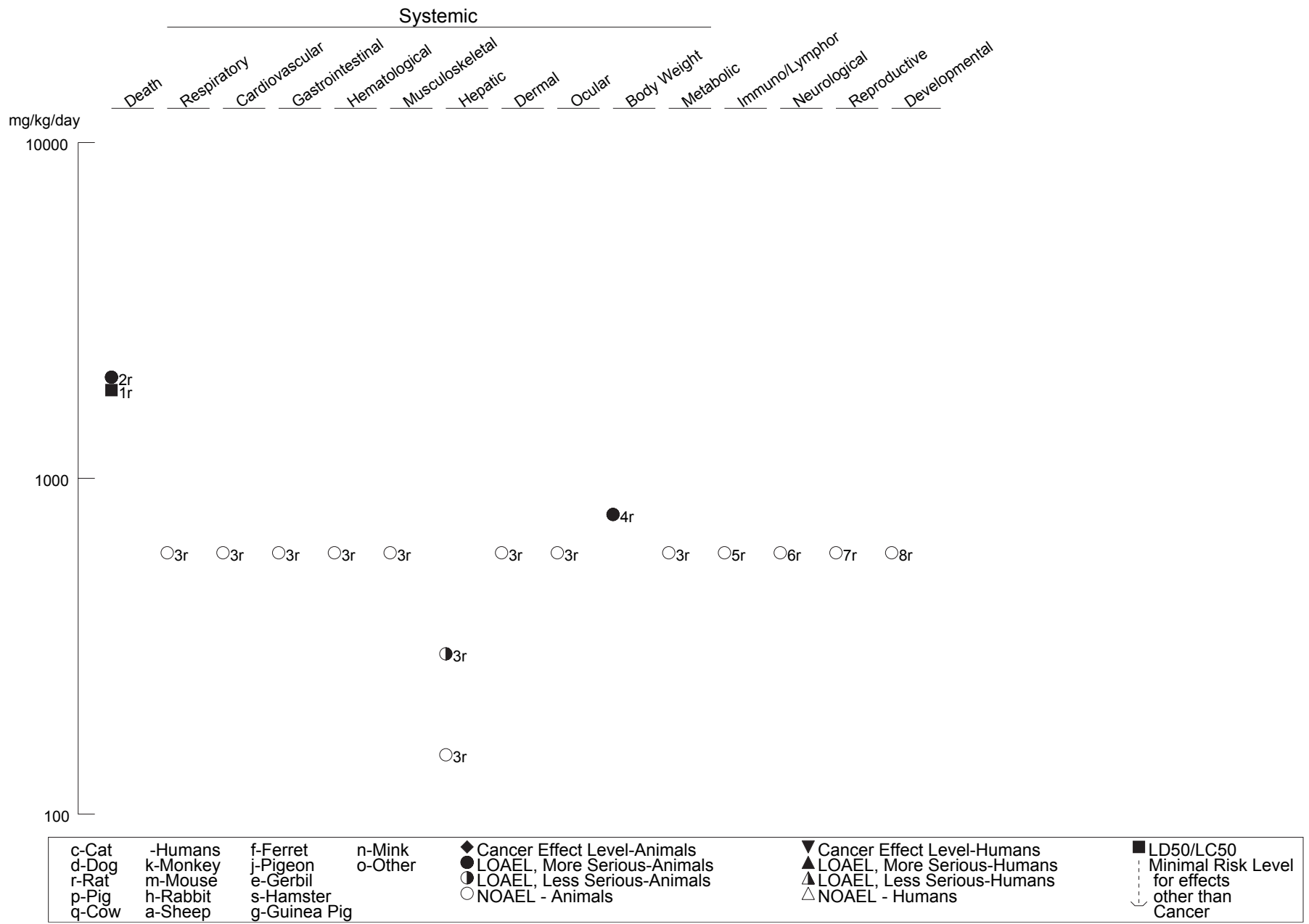


Figure 3-4 Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Oral (Continued)
Intermediate (15-364 days)

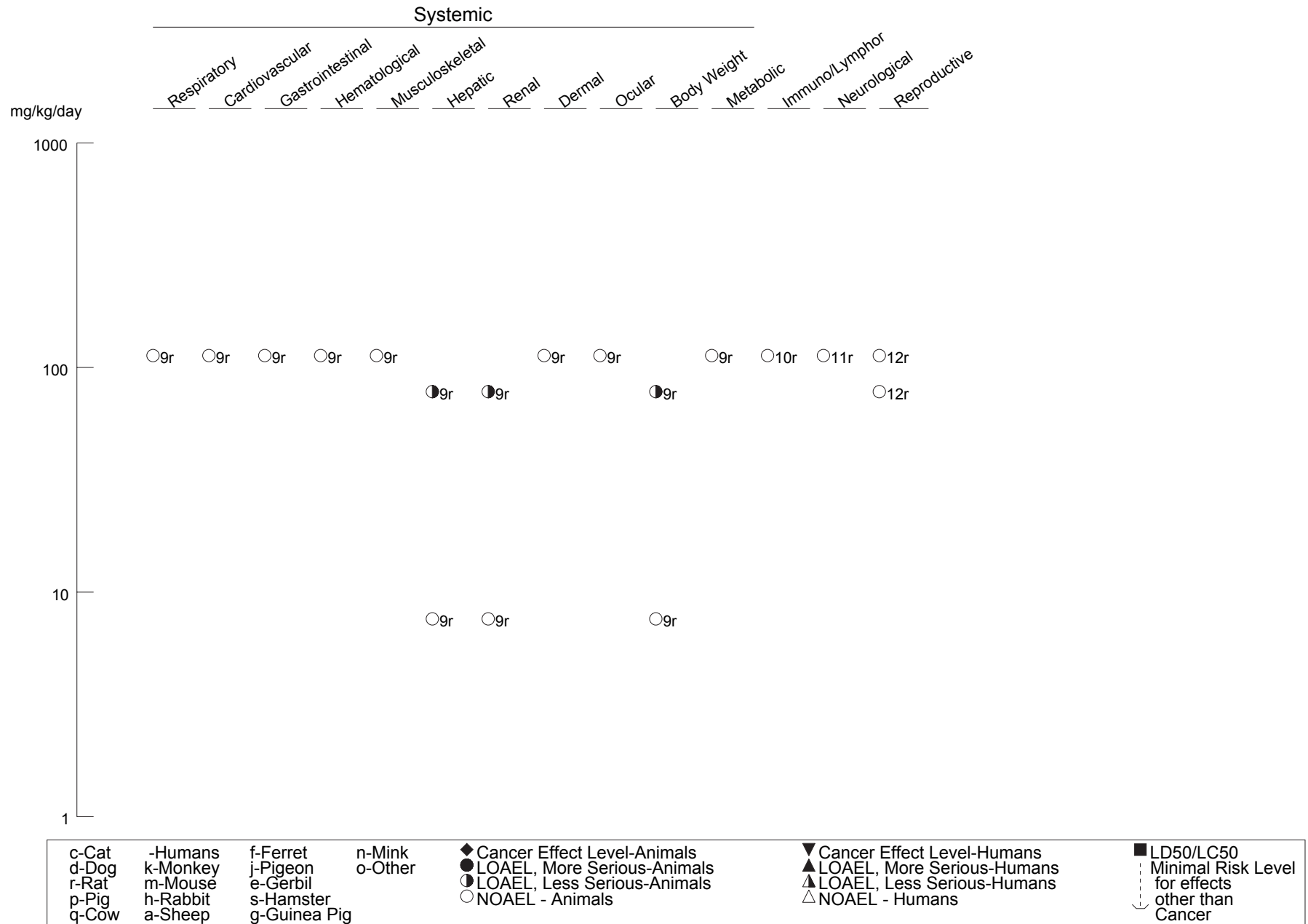


Table 3-5 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (F)				2100 (LD50)	Cote et al. 1988 1,3,5-Trichlorobenzene	
2	Rat (Sprague-Dawley)	once (GO)				1800 M (LD50) 2800 F (LD50)	Jorgenson et al. 1976 1,3,5-Trichlorobenzene	
3	Mouse (ICR)	once (GO)				3350 M (LD50) 3402 F (LD50)	Jorgenson et al. 1976 1,3,5-Trichlorobenzene	
Systemic								
4	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)	Resp	600 F			Black et al. 1988 1,3,5-Trichlorobenzene	NOAELs are for organ and tissues histopathology
			Cardio	600 F				
			Gastro	600 F				
			Hemato	600 F				
			Musc/skel	600 F				
			Hepatic	300 F	600 F (25% increase in relative liver weight)			
			Dermal	600 F				
			Ocular	600 F				
			Bd Wt	300 F		600 F (34% reduced body weight gain)		
			Metab	600 F				

Table 3-5 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Immuno/ Lymphoret								
5	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		600 F			Black et al. 1988 1,3,5-Trichlorobenzene	NOAEL is for spleen and thymus histopathology
Neurological								
6	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		600 F			Black et al. 1988 1,3,5-Trichlorobenzene	NOAEL is for histopathology of the brain and peripheral nerve
Reproductive								
7	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		600 F			Black et al. 1988 1,3,5-Trichlorobenzene	NOAEL is for histopathology of reproductive organs
Developmental								
8	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)			150	(histological lesions in the lenses of pups)	Black et al. 1988 1,3,5-Trichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
INTERMEDIATE EXPOSURE								
Systemic								
9	Rat (Sprague- Dawley)	13 wk ad lib (F)	Resp	146 F			Cote et al. 1988 1,3,5-Trichlorobenzene	NOAELs are for organ histopathology
			Cardio	146 F				
			Gastro	146 F				
			Hemato	146 F				
			Musc/skel	146 F				
			Hepatic	7.7 M	82 M	11% increase in relative liver weight)		
			Renal	0.81 M	7.7 M	25% increase in relative kidney weight)		
			Dermal	146 F				
			Ocular	146 F				
			Bd Wt	146 F				
			Metab	146 F				
Immuno/ Lymphoret								
10	Rat (Sprague- Dawley)	13 wk ad lib (F)		146 F			Cote et al. 1988 1,3,5-Trichlorobenzene	NOAEL is for histopathology of lymphoreticular organs and tissues
Neurological								
11	Rat (Sprague- Dawley)	13 wk ad lib (F)		146 F			Cote et al. 1988 1,3,5-Trichlorobenzene	NOAEL is for histopathology of brain, spinal cord and sciatic nerve

Table 3-5 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Reproductive								
12	Rat (Sprague- Dawley)	13 wk ad lib (F)		82 M 146 F			Cote et al. 1988 1,3,5-Trichlorobenzene	NOAEL is for histopathology of reproductive organs

^a The number corresponds to entries in Figure 3-5.

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-5 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral
Acute (≤14 days)

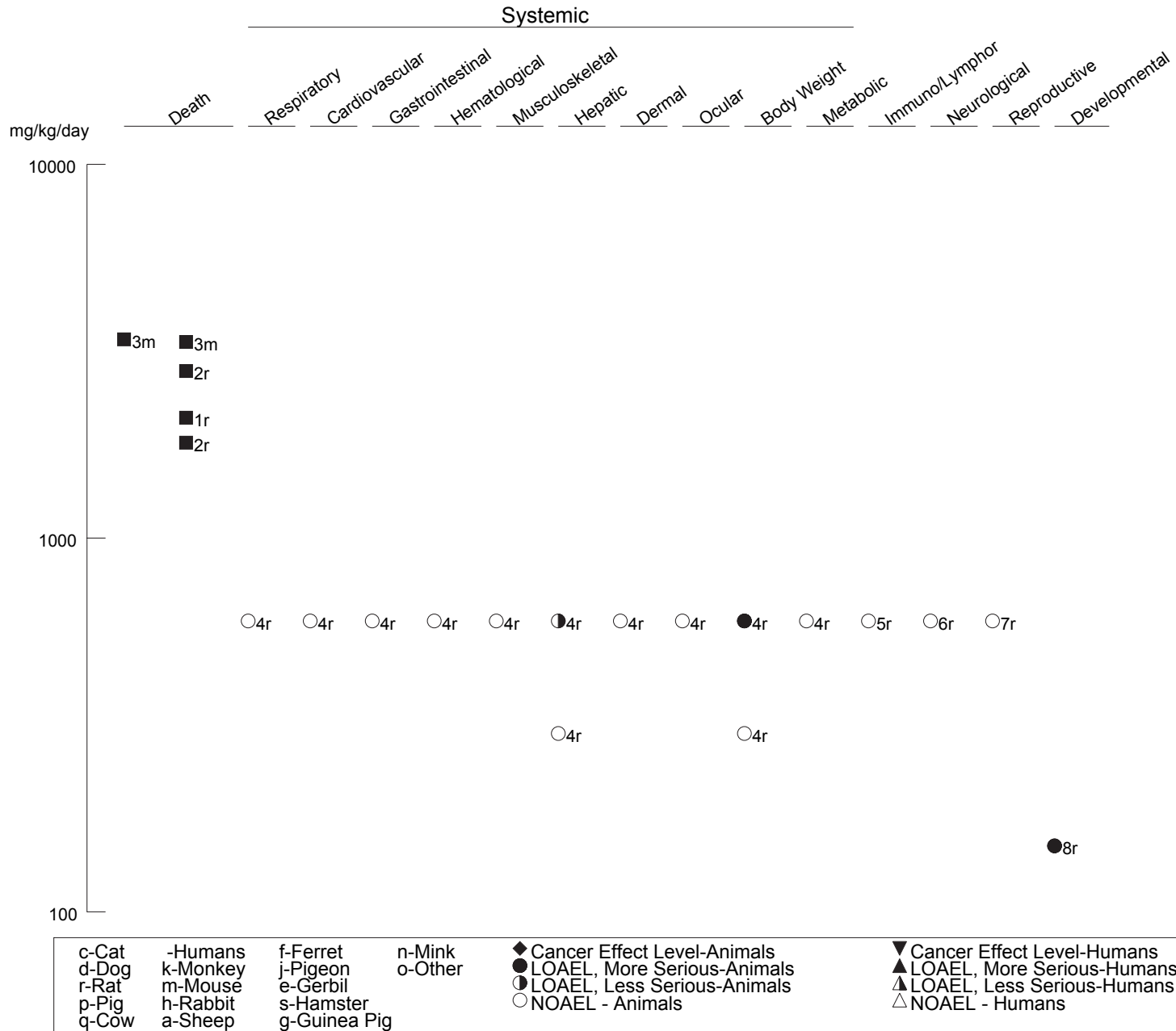
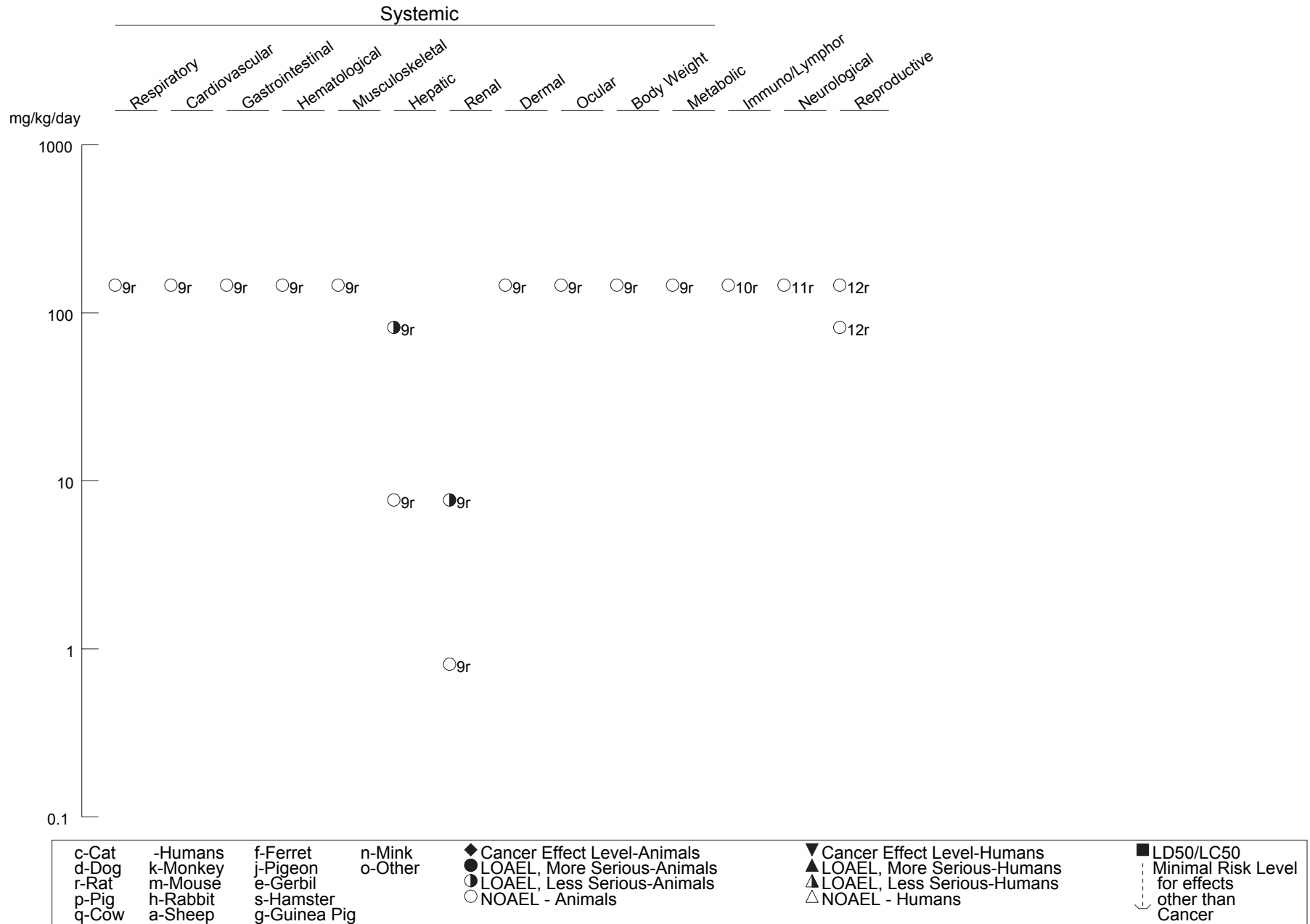


Figure 3-5 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Oral (Continued)
Intermediate (15-364 days)



3. HEALTH EFFECTS

studies, there were also no significant histological alterations in the lungs, trachea, or bronchi from rats exposed via the diet to up to 101 mg/kg/day (Côté et al. 1988) or 150.6 mg/kg/day (CMA 1989) 1,2,4-trichlorobenzene. A 13-week dietary study in mice reported no significant histological alterations in the lungs or trachea from animals dosed with up to 1,345 mg/kg/day 1,2,4-trichlorobenzene (Hiles 1989). Chronic-duration exposure to 1,2,4-trichlorobenzene also did not induce significant histological alterations in the lungs and trachea from rats dosed via the diet with up to 81.4 mg/kg/day 1,2,4-trichlorobenzene (Moore 1994a) or from mice dosed with up to 572.6 mg/kg/day 1,2,4-trichlorobenzene (Moore 1994b).

Black et al. (1988) also studied the 1,2,3- and 1,3,5- isomers and reported no significant effects in the lungs, bronchi, and trachea of pregnant rats dosed by gavage with up to 600 mg/kg/day of either isomer on Gd 6–15 and sacrificed on Gd 22. Similar results were reported in rats treated with up to 113 mg/kg/day 1,2,3-trichlorobenzene or 146 mg/kg/day 1,3,5-trichlorobenzene in the diet for 13 weeks (Côté et al. 1988).

Cardiovascular Effects. No significant gross or microscopic alterations were observed in the heart of rats dosed by gavage with up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3- or 1,3,5-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22 (Black et al. 1988). Similar results were reported regarding the heart and aorta from rats treated with up to 101 mg/kg/day 1,2,4-trichlorobenzene, 113 mg/kg/day 1,2,3-trichlorobenzene, or 146 mg/kg/day 1,3,5-trichlorobenzene in the diet for 13 weeks (Côté et al. 1988), or 150.6 mg/kg/day 1,2,4-trichlorobenzene for 14 weeks (CMA 1989). Treatment of mice with up to 1,345 mg/kg/day 1,2,4-trichlorobenzene for 13 weeks via the diet did not significantly alter the gross or microscopic appearance of the heart or aorta (Hiles 1989). Treatment of rats with up to 81.4 mg/kg/day 1,2,4-trichlorobenzene or mice with up to 572.6 mg/kg/day 1,2,4-trichlorobenzene through the diet for 104 weeks did not induce gross or microscopic changes in the heart (Moore 1994a, 1994b).

Gastrointestinal Effects. No significant gross or microscopic alterations were reported in the gastrointestinal tract of rats dosed by gavage with up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3- or 1,3,5-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22 (Black et al. 1988). Similar results were reported in rats treated with up to 101 mg/kg/day 1,2,4-trichlorobenzene, 113 mg/kg/day 1,2,3-trichlorobenzene, or 146 mg/kg/day 1,3,5-trichlorobenzene in the diet for 13 weeks (Côté et al. 1988), or 150.6 mg/kg/day 1,2,4-trichlorobenzene for 14 weeks (CMA 1989). Examination of the gastrointestinal tract from mice dosed with up to 1,345 mg/kg/day 1,2,4-trichlorobenzene for

3. HEALTH EFFECTS

13 weeks via the diet did not reveal significant treatment-related gross or histological alterations (Hiles 1989). No gross or histological alterations were reported in the gastrointestinal tract from rats or mice dosed via the diet with up to 81.4 or 572.6 mg/kg/day 1,2,4-trichlorobenzene, respectively for 104 weeks (Moore 1994a, 1994b).

Hematological Effects. Changes in hematological parameters have been reported in some acute- and intermediate-duration studies. However, since the reductions in hemoglobin and hematocrit reported in some of these studies are within the normal range for these parameters, they are not listed as LOAELs in Table 3-2; instead, the highest doses tested are listed as NOAELs for hematological effects.

Treatment of pregnant rats with 150 or 300 mg/kg/day 1,2,4-trichlorobenzene during Gd 6–15 resulted in reductions in hemoglobin (6–7%) and hematocrit (6%) (Black et al. 1988). In the same study, doses of 300 and 600 mg/kg/day 1,2,3-trichlorobenzene reduced hemoglobin by 6–7% and doses of 600 mg/kg/day reduced the hematocrit by approximately 6%. Rats treated with 600 mg/kg/day 1,3,5-trichlorobenzene showed reduction in hemoglobin and hematocrit of approximately 10–11% (Black et al. 1988). In another acute-duration study in rats, doses of up to 40 mg/kg/day 1,2,4-trichlorobenzene by gavage for 14 days did not affect hemoglobin or hematocrit levels (Carlson and Tardiff 1976).

Some intermediate-duration dietary studies have reported mild hematological changes following exposure to 1,2,4-trichlorobenzene. For example, treatment of male rats with 133.7 mg/kg/day, but not 45.6 mg/kg/day, 1,2,4-trichlorobenzene in the diet for 14 weeks reduced mean erythrocyte count (5%), hemoglobin (1.2%), and hematocrit (6%) (CMA 1989). In female rats, doses of 150.6 mg/kg/day reduced hemoglobin and hematocrit by 3.6–4%. Platelets were increased in males dosed with 133.7 mg/kg/day. In a similar study, administration of doses of up to 82 mg/kg/day to male rats and 101 mg/kg/day to females did not alter hematological parameters (Côté et al. 1988). No significant hematological changes were observed in male mice dosed with up to 1,222 mg/kg/day 1,2,4-trichlorobenzene for 13 weeks (Hiles 1989). In the same study, female mice dosed with 1,345 mg/kg/day 1,2,4-trichlorobenzene had lower (5–9%) hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin; since these changes occurred only in females, the investigator (Hiles 1989) did not consider them to be treatment-related.

Administration in the diet of up to 113 mg/kg/day 1,2,3-trichlorobenzene or 146 mg/kg/day 1,3,5-trichlorobenzene to rats for 13 weeks did not alter hematological parameters (Côté et al. 1988).

3. HEALTH EFFECTS

In the chronic-duration oral studies with 1,2,4-trichlorobenzene, cellular morphology and leukocyte differential were monitored on weeks 52, 78, and at termination (Moore 1994a, 1994b). The results showed no significant treatment-related alterations in the parameters monitored in rats dosed through the diet with up to 81.4 mg/kg/day or in mice dosed with up to 572.6 mg/kg/day 1,2,4-trichlorobenzene. No evidence of leukemia was seen in either study.

Musculoskeletal Effects. No significant gross or histological alterations were reported in skeletal muscle from pregnant rats dosed with up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22 (Black et al. 1988).

Similar results were reported in rats dosed via the diet with up to 150.6 mg/kg/day 1,2,4-trichlorobenzene, 113 mg/kg/day 1,2,3-trichlorobenzene, or 146 mg/kg/day 1,3,5-trichlorobenzene for 3 months (CMA 1989; Côté et al. 1988). An intermediate-duration dietary study in mice dosed with up to 1,345 mg/kg/day 1,2,4-trichlorobenzene for 13 weeks also did not find morphological alterations in bone or skeletal muscle (Hiles 1989). Chronic-duration studies did not find morphological alterations in bone or skeletal muscle from rats or mice dosed with up to 81.4 or 572.6 mg/kg/day 1,2,4-trichlorobenzene via the diet, respectively, for 104 weeks (Moore 1994a, 1994b).

Hepatic Effects. Acute-, intermediate-, and chronic-duration oral studies in animals indicate that the liver is a target for trichlorobenzenes. An acute-duration study with 1,2,4-trichlorobenzene described intense necrosis and fatty change in rats following administration of 500 mg/kg/day 1,2,4-trichlorobenzene by gavage for 10 days (Rimington and Ziegler 1963). In a 14-day gavage study in male rats, 1,2,4-trichlorobenzene induced a dose-related increase in relative liver weight (all doses, 15.3% at 10 mg/kg/day, 28.9% at 40 mg/kg/day) (Carlson and Tardiff 1976). Moderate hepatocellular hypertrophy was reported in the liver from pregnant rats following administration of 360 mg/kg/day for 4 days; the NOAEL for this effect was 120 mg/kg/day (Kitchin and Ebron 1983). In another developmental study, mild hepatic changes consisting of increased periportal cytoplasmic eosinophilia and mild anisokaryosis of hepatocellular nuclei were reported in pregnant rats dosed with 150 and 300 mg/kg/day 1,2,4-trichlorobenzene on Gd 6–15 (Black et al. 1988). The same was reported in pregnant rats dosed with 300 and 600 mg/kg/day 1,2,3- or 1,3,5-trichlorobenzene. Because no quantitative histological data were presented in the latter study, this information is not listed in Tables 3-3, 3-4, and 3-5. Histological alterations in the liver were almost always accompanied by increases in liver weight.

3. HEALTH EFFECTS

In a 90-day study in male rats, gavage administration of 1,2,4-trichlorobenzene (10, 20, 40 mg/kg/day) increased relative liver weight 14% in high-dose rats after a 30-day recovery period; however, no significant histological alterations were seen in the liver (Carlson and Tardiff 1976). Dietary administration of ≥ 14.6 mg/kg/day 1,2,4-trichlorobenzene to male rats or ≥ 52.5 mg/kg/day to females for 14 weeks induced dose-related increases in absolute and relative liver weights (CMA 1989). Microscopic examination of the liver revealed an increased incidence of centrilobular hepatocyte hypertrophy in male rats dosed with ≥ 45.6 mg/kg/day 1,2,4-trichlorobenzene and in female rats dosed with 150.6 mg/kg/day; the corresponding NOAELs were 14.6 and 52.5 mg/kg/day (CMA 1989). Centrilobular hepatocyte hypertrophy was used as the basis for derivation of an intermediate-duration oral MRL for 1,2,4-trichlorobenzene. An additional intermediate-duration dietary study reported significant increases in relative liver weight in male rats dosed with 78–82 mg/kg/day of each trichlorobenzene isomer (Côté et al. 1988). The investigators stated that most treated groups (doses ranged from approximately 0.1 to 140 mg/kg/day) showed mild-to-moderate increases in cytoplasmic volume and anisokaryosis of hepatocytes mostly in perivenous and midzone areas. High-dose rats showed aggregated basophilia as well as widespread midzonal vacuolation due to fatty infiltration. However, since only a qualitative description of the histological changes was provided, it is impossible to determine with certainty NOAELs or LOAELs for the lesions; therefore, they are not listed in Tables 3-3, 3-4, or 3-5, but the organ weight changes are.

A significant increase in absolute and relative liver weight was reported in male mice dosed via the diet with ≥ 850 mg/kg/day 1,2,4-trichlorobenzene and female mice dosed with $\geq 1,183$ mg/kg/day 1,2,4-trichlorobenzene for 13 weeks (Hiles 1989). These changes in liver weight correlated with microscopic changes characterized by hepatocellular cytomegaly with karyomegaly and multinucleation complex with adjacent hepatocellular compression, atrophy, anisocytosis, vacuolar degeneration, and necrosis. The NOAELs for these alterations were 67 and 86 mg/kg/day in males and females, respectively. In addition, changes in clinical chemistry that were considered treatment-related consisted of higher total protein in mid-dose males (850 mg/kg/day) and high-dose males (1,222 mg/kg/day) and females (1,345 mg/kg/day), increased albumin and globulin in high-dose males and females, increased serum alanine aminotransferase (ALT) in mid-dose males and in high-dose males and females, and increased sorbitol dehydrogenase (SDH) in mid- and high-dose males and females. According to the investigators, the higher protein was probably caused by dehydration.

In a 104-week dietary study with 1,2,4-trichlorobenzene in rats, doses of 66.5 mg/kg/day in males and 81.4 mg/kg/day in females produced significant increases in absolute and relative liver weight at termination (Moore 1994a). The corresponding NOAELs were 19.4 and 23.5 mg/kg/day. Significant

3. HEALTH EFFECTS

increases in the incidence of liver lesions were reported in rats that received the highest doses, 66.5 mg/kg/day in males and 81.4 mg/kg/day in females. The histological alterations consisted of hepatocyte hypertrophy, focal cystic degeneration, and diffuse fatty change. The increased incidence of hepatocyte hypertrophy in male rats served as the basis for derivation of a chronic-duration oral MRL for 1,2,4-trichlorobenzene. In a similar study in mice, doses ≥ 21 mg/kg/day 1,2,4-trichlorobenzene induced a dose-related increase in absolute and relative liver weight in males, whereas doses ≥ 100.6 mg/kg/day 1,2,4-trichlorobenzene increased relative liver weight (Moore 1994b). In females, doses ≥ 26.3 mg/kg/day also increased absolute and relative liver weight. Histological examination of the liver showed a significant increase in the incidence of centrilobular hepatocytomegaly in males dosed with ≥ 101 mg/kg/day 1,2,4-trichlorobenzene. The neoplastic effects in mice are described in Section 3.2.2.7, Cancer.

In addition to inducing changes in liver weight and morphological alterations in the liver, 1,2,4-trichlorobenzene has been shown to be a potent inducer of phase I and phase II metabolic enzymes (Ariyoshi et al. 1975a, 1975b; Carlson and Tardiff 1976; Kato and Kimura 2002; Kato et al. 1988, 1993; Kitchin and Ebron 1983). For example, administration of ≥ 10 mg/kg/day 1,2,4-trichlorobenzene to rats by gavage for 14 days resulted in dose-related increases in cytochrome c reductase, cytochrome P-450, glucuronyl-transferase, EPN detoxification, and azoreductase (Carlson and Tardiff 1976). Extending the dosing period to 90 days resulted in smaller increases in enzyme activities, except for glucuronyltransferase activity, which was reduced relative to controls (Carlson and Tardiff 1976). In rats, 1,2,4-trichlorobenzene also induced ALA synthetase, the rate-limiting enzyme in the biosynthesis of heme, which is consistent with the development of porphyria in rats administered 1,2,4-trichlorobenzene (Rimington and Ziegler 1963). For example, doses of 250–500 mg/kg/day significantly increased the urinary excretion of coproporphyrin and, to a smaller extent, the excretion of uroporphyrins. Liver uroporphyrin was also increased by 1,2,4-trichlorobenzene; liver coproporphyrin and protoporphyrin were increased in rats showing marked porphyrinuria. Studies by Kato and coworkers (Kato and Kimura 2002; Kato et al. 1988, 1993) have shown that both the induction of drug-metabolizing enzymes and ALA synthetase are not due to 1,2,4-trichlorobenzene itself but its metabolite 2,3,5-trichlorophenyl methyl sulfone. Further information on the mechanism of porphyria can be found in Section 3.5, Mechanisms of Action.

Renal Effects. No gross or microscopic alterations were reported in the kidneys from pregnant rats dosed on Gd 6–15 with up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene and sacrificed on Gd 22 (Black et al. 1988).

3. HEALTH EFFECTS

In a 13-week dietary study in rats with trichlorobenzenes, the three isomers increased relative kidney weight in male rats in doses ranging between 78 and 82 mg/kg/day (no data on females were presented), but only 1,3,5-trichlorobenzene reportedly induced morphological alterations in the kidneys (Côté et al. 1988). The changes were characterized by eosinophilic inclusion, enlargement and anisokariosis of the epithelial lining cells, and hyperplasia of renal tubular epithelial cells. Only the changes associated with the highest dose levels, 78–82 mg/kg/day, were considered to be biologically significant by the investigators. Since only a qualitative description of the histology was provided, NOAELs and LOAELs for histological changes are not presented in Tables 3-3, 3-4, and 3-5, but the organ weight changes are. In a 14-week dietary study with 1,2,4-trichlorobenzene in rats, doses ≥ 45.6 mg/kg/day in males and ≥ 52.5 mg/kg/day in females significantly increased relative kidney weight, but morphological alterations were seen only in high-dose males (133.7 mg/kg/day) and consisted of dilated tubules, granular casts, hyaline droplets, and interstitial nephritis (CMA 1989). BUN was also significantly elevated in high-dose males and females (150.6 mg/kg/day). Mice administered up to 1,345 mg/kg/day 1,2,4-trichlorobenzene via the diet for 13 weeks did not show significant gross or microscopic alterations in the kidneys (Hiles 1989).

In the 104-week dietary studies with 1,2,4-trichlorobenzene in rats and mice, kidney alterations were reported only in rats (Moore 1994a). Gross necropsy at termination showed increases incidence of kidney abnormalities in mid- (19.4 mg/kg/day) and high-dose (66.5 mg/kg/day) males. Microscopically, there was an increased incidence in marked renal papilla mineralization in high-dose males and in transitional renal cell hyperplasia, also in males; only the latter effect showed dose-response. In addition, there was an increase in severity of chronic nephropathy in males. In mice, there were no significant gross or microscopic alterations in the kidneys following dosing with up to 572.6 mg/kg/day 1,2,4-trichlorobenzene (Moore 1994b).

Endocrine Effects. The only relevant information from acute-duration exposures is that from the study by Black et al. (1988) in which pregnant rats were administered trichlorobenzenes by gavage on Gd 6–15 and were sacrificed on Gd 22. No significant gross or microscopic alterations were reported in the pituitary, parathyroid, adrenals, or pancreas from dams following doses of up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene. However, mild thyroid histopathology was reported in rats dosed with ≥ 300 mg/kg/day of each isomer; the NOAEL in each case was 150 mg/kg/day. The alterations were described as reduction of follicle size and increased epithelial height accompanied by cytoplasmic vacuolization. Since no quantitative data were presented, NOAELs and LOAELs for thyroid effects are not presented in Tables 3-3, 3-4, and 3-5.

3. HEALTH EFFECTS

Côté et al. (1988) examined the same organs in a 13-week study in Sprague-Dawley rats and reported similar results. Morphological alterations were limited to the thyroid and were described as mild and appeared to be more severe in males. Reported changes consisted of reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape, and reduced colloid density. Changes in the high-dose groups (78–82 mg/kg/day) varied from mild to moderate. Since no quantitative data were presented, NOAELs and LOAELs for histological alterations in the thyroid are not listed in Tables 3-3, 3-4, and 3-5. In contrast, CMA (1989) did not find significant histological alterations in the thyroid from Fisher-344 rats dosed with up to 150.6 mg/kg/day 1,2,4-trichlorobenzene in the diet for 14 weeks. Whether this can be attributed to differences in sensitivity between rat strains is unknown. No significant alterations were reported in endocrine glands from mice dosed via the diet with up to 1,345 mg/kg/day 1,2,4-trichlorobenzene for 13 weeks (Hiles 1989) or from rats or mice dosed with up to 81.4 or 572.6 mg/kg/day 1,2,4-trichlorobenzene, respectively, for 104 weeks (Moore 1994a, 1994b).

Dermal Effects. None of the studies that examined the skin of animals following oral administration of trichlorobenzenes reported treatment-related gross or microscopic alterations. These include the acute developmental study by Black et al. (1988) (300 mg/kg/day 1,2,4-trichlorobenzene; 600 mg/kg/day 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene), a 13-week dietary study (Côté et al. 1988) (78–82 mg/kg/day), and 104-week dietary studies with 1,2,4-trichlorobenzene in rats (Moore 1994a) (81.4 mg/kg/day) and mice (Moore 1994b) (572.6 mg/kg/day).

Ocular Effects. Examination of the eyes of animals exposed orally to trichlorobenzenes did not show treatment-related gross or histological alterations. These include the acute developmental study by Black et al. (1988; 300 mg/kg/day 1,2,4-trichlorobenzene; 600 mg/kg/day 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene), 3-month dietary studies in rats (Côté et al. 1988; 78–82 mg/kg/day, and CMA 1989; 150.6 mg/kg/day), a 13-week dietary study with 1,2,4-trichlorobenzene in mice (Hiles 1989; 1,345 mg/kg/day), and 104-week dietary studies with 1,2,4-trichlorobenzene in rats (Moore 1994a; 81.4 mg/kg/day) and mice (Moore 1994b; 572.6 mg/kg/day).

Body Weight Effects. Almost all studies of trichlorobenzenes monitored body weight of the animals. Pregnant rats administered 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3-trichlorobenzene on Gd 6–15 gained less weight than controls, but quantitative data for these isomers were not provided (Black et al. 1988). However, administration of 600 mg/kg/day 1,3,5-trichlorobenzene resulted in a reduction in weight gain of 34% relative to controls on Gd 22 (Black et al. 1988). In another

3. HEALTH EFFECTS

developmental study, doses of 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 induced weight loss; 120 mg/kg/day had no significant effect (Kitchin and Ebron 1983). Weight loss was also reported in a study in rats dosed by gavage with 500 mg/kg/day 1,2,4-trichlorobenzene for 10 days or with 780 mg/kg/day 1,2,3-trichlorobenzene for 7 day (Rimington and Ziegler 1963). None of these studies provided information on food consumption.

Fifteen days of dosing with 730 mg/kg/day 1,2,4-trichlorobenzene by gavage resulted in loss of appetite and weight loss in rats (Rimington and Ziegler 1963). Neither food consumption nor weight gain was significantly affected in rats dosed via the diet with up to 101 mg/kg/day 1,2,4-trichlorobenzene or 146 mg/kg/day 1,3,5-trichlorobenzene for 13 weeks (Côté et al. 1988). Similar results were reported in rats dosed through the diet with up to 150.6 mg/kg/day 1,2,4-trichlorobenzene for 14 weeks (CMA 1989). Male rats treated with 78 mg/kg/day 1,2,3-trichlorobenzene for 13 weeks gained 10.2% less weight than controls (Côté et al. 1988); the NOAEL was 7.6 mg/kg/day. Final body weight was significantly reduced in male mice dosed with 1,222 mg/kg/day 1,2,4-trichlorobenzene (9%) and in female mice dosed via the diet with 1,345 mg/kg/day 1,2,4-trichlorobenzene (8.3%) for 13 weeks (Hiles 1989). Cumulative body weight gain was significantly reduced in males dosed with 67 mg/kg/day 1,2,4-trichlorobenzene (27%), in males dosed with 1,222 mg/kg/day 1,2,4-trichlorobenzene (40%), and in females dosed with 1,345 mg/kg/day 1,2,4-trichlorobenzene (33%); these changes were associated with significant reductions in food consumption throughout the study.

Final body weight of rats dosed through the diet with up to 81.4 mg/kg/day 1,2,4-trichlorobenzene for 104 weeks was not significantly different than controls (Moore 1994a). Final body weight of male mice dosed with 519.9 mg/kg/day 1,2,4-trichlorobenzene in the diet for 104 weeks was 16% lower than controls; food consumption in this group was reduced during the first 52 weeks of the study (Moore 1994b). Final body weight was not significantly affected in female mice dosed with up to 572.6 mg/kg/day 1,2,4-trichlorobenzene. The NOAEL for body weight changes in male mice was 100.6 mg/kg/day.

Metabolic Effects. Administration of up to 300 mg/kg/day 1,2,4-trichlorobenzene or up to 600 mg/kg/day 1,2,3- or 1,3,5-trichlorobenzene to pregnant rats on Gd 6–15 did not significantly alter the concentration of electrolytes or glucose in blood (Black et al. 1988).

None of the intermediate-duration studies with trichlorobenzenes reported adverse metabolic effects. Treatment of rats with dietary doses of up to 150.6 mg/kg/day or mice with up to 1,345 mg/kg/day

3. HEALTH EFFECTS

1,2,4-trichlorobenzene for 3 months had no significant effect on serum electrolyte or glucose levels (CMA 1989; Côté et al. 1988; Hiles 1989). Similar results were reported in rats dosed via the diet with up to 113 mg/kg/day 1,2,3-trichlorobenzene or 146 mg/kg/day 1,3,5-trichlorobenzene (Côté et al. 1988).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to trichlorobenzenes.

Information from studies in animals is limited to evaluations of the gross and microscopic morphology of lymphoreticular organs and tissues. In pregnant rats that were exposed to up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene on Gd 6–15, there were no significant morphological changes in the spleen or thymus on Gd 22 (Black et al. 1988).

Intermediate-duration studies showed that exposure of rats to up to 150.6 mg/kg/day 1,2,4-trichlorobenzene, 113 mg/kg/day 1,2,3-trichlorobenzene, or 146 mg/kg/day 1,3,5-trichlorobenzene, or mice to up to 1,345 mg/kg/day 1,2,4-trichlorobenzene in the diet for 3 months did not alter the gross or microscopic morphology of the spleen, thymus, or lymph nodes (CMA 1989; Côté et al. 1988). Similar results were reported in rats and mice dosed with up to 81.4 and 572.6 mg/kg/day 1,2,4-trichlorobenzene, respectively, in the diet for 104 weeks (Moore 1994a, 1994b).

These values are presented as NOAELs for lymphoreticular effects in Table 3-3, 3-4, and 3-5 and are plotted in Figures 3-3, 3-4, and 3-5.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to trichlorobenzenes.

No gross or histological alterations were observed in the brain and peripheral nerves from rats exposed to up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22 (Black et al. 1988).

Côté et al. (1988) examined the brain, spinal cord, and sciatic nerve from rats following a 13-week exposure period via the diet to doses of up to 101 mg/kg/day 1,2,4-trichlorobenzene, 113 mg/kg/day

3. HEALTH EFFECTS

1,2,3-trichlorobenzene, or 146 mg/kg/day 1,3,5-trichlorobenzene and reported no significant gross or microscopic alterations in those tissues. Similar results were reported in rats dosed via the diet with up to 150.6 mg/kg/day 1,2,4-trichlorobenzene for 14 weeks (CMA 1989) and in mice dosed with up to 1,345 mg/kg/day 1,2,4-trichlorobenzene for 13 weeks (Hiles 1989). Dietary exposure of rats and mice to up to 81.4 and 572.6 mg/kg/day 1,2,4-trichlorobenzene, respectively, in the diet for 104 weeks also did not induce histological alterations in the brain, spinal cord, or sciatic nerve (Moore 1994a, 1994b).

The NOAELs for morphological changes in the central and peripheral nervous systems are listed in Tables 3-3, 3-4, and 3-5 and are plotted in Figures 3-3, 3-4, and 3-5.

3.2.2.5 Reproductive Effects

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

Examination of the ovaries and uteri from rats dosed by gavage with up to 300 mg/kg/day 1,2,4-trichlorobenzene or 600 mg/kg/day 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22 did not show significant gross or microscopic alterations (Black et al. 1988).

No treatment-related morphological alterations were reported in the reproductive organs from male or female rats dosed via the diet with 1,2,4-trichlorobenzene (82 mg/kg/day males, 101 mg/kg/day females), 1,2,3-trichlorobenzene (78 mg/kg/day males, 113 mg/kg/day females), or 1,3,5-trichlorobenzene (82 mg/kg/day males, 146 mg/kg/day females) for 13 weeks (Côté et al. 1988). No alterations were noted in the reproductive organs from male and female rats dosed via the diet with up to 133.7 and 150.6 mg/kg/day 1,2,4-trichlorobenzene, respectively, for 14 weeks (CMA 1989) or male and female mice dosed with up to 1,222 and 1,345 mg/kg/day, respectively, for 13 weeks (Hiles 1989).

Two-year dietary studies with 1,2,4-trichlorobenzene in rats (66.5 mg/kg/day males, 81.4 mg/kg/day females) and mice (519.9 mg/kg/day males, 572.6 mg/kg/day females) also did not find gross or microscopic alterations in the reproductive organs (Moore 1994a, 1994b).

Robinson et al. (1981) conducted a multi-generation reproductive study in rats in which the F0 and F1 generations were exposed to 1,2,4-trichlorobenzene via the mother's milk until weaning and then directly through their drinking water. At approximately 90 days of age in the F0 and F1 generations, the rats were

3. HEALTH EFFECTS

mated to produce the subsequent generation. The results showed that treatment of males and females with up to 33 or 53.6 mg/kg/day 1,2,4-trichlorobenzene, respectively, did not affect fertility. The doses correspond to the intake of test material by the F0 generation at 83 days of age and were estimated by the investigators.

The NOAELs for reproductive organs histology and the NOAEL for fertility from Robinson et al. (1981) are presented in Tables 3-3, 3-4, and 3-5 and are plotted in Figures 3-3, 3-4, and 3-5.

3.2.2.6 Developmental Effects

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

Black et al. (1988) examined the developmental effects of trichlorobenzenes in Sprague-Dawley rats. Rats were administered 0, 75, 150, or 300 mg/kg/day 1,2,4-trichlorobenzene or 0, 150, 300, or 600 mg/kg/day 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene by gavage in corn oil on Gd 6–15. Dams were sacrificed on Gd 22, and the uterus and ovaries were removed. Fetuses were examined grossly for birth defects and were also examined for skeletal and visceral anomalies. Also, entire fetuses were fixed, stained, and examined microscopically. Gestational exposure to the trichlorobenzenes did not significantly alter the number of pregnancies, fetal weight, litter size, resorptions, or dead fetuses, or the incidences of skeletal and visceral anomalies. However, fetuses from the 150 mg/kg/day 1,2,4-trichlorobenzene group and all groups exposed to 1,3,5-trichlorobenzene showed histological alterations in the lenses of the eye consisting of central areas of cellular disorientation and disaggregation with ballooning and granular degeneration. The investigators stated that autolysis and incomplete preservation made examination of other fetal tissues difficult, but there did not appear to be any significant treatment-related changes. In an additional study, pregnant rats were dosed with 0 or 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 and were sacrificed on Gd 14 (Kitchin and Ebron 1983). Treatment did not increase resorptions or induce significant embryoletality or teratogenicity; however, it significantly retarded development as measured by reduced head length, crown-rump length, somite number, and protein content. It should be noted that dams administered 360 mg/kg/day 1,2,4-trichlorobenzene lost considerable body weight, which probably contributed to the delayed development of the offspring.

A series of studies were conducted with 1,2,4-trichlorobenzene in which pregnant mice were administered 0 or 130 mg/kg/day 1,2,4-trichlorobenzene by gavage on Gd 8–12 (Chernoff and Kavlock 1983; Gray and

3. HEALTH EFFECTS

Kavlock 1984; Gray et al. 1986). Treatment with 1,2,4-trichlorobenzene had no significant effect on average litter weight, pup viability, or growth. Testing of the pups in a figure 8 maze for reactive locomotor activity levels on postnatal days 22, 58, and 200 showed no significant differences between pups from treated groups and controls. Examination of female pups at age 30 days showed no significant effect on percent vaginal patency. Breeding of the F1 pups resulted in no significant effects on percent pregnant, age at parturition, F2 litter size, or abnormalities in the F2 generation. Necropsy of F1 males at about 250 days of age showed no significant effects on body weight and weight of the liver, testes, seminal vesicles, or right kidneys.

In the multi-generation reproductive study conducted by Robinson et al. (1981), treatment with 1,2,4-trichlorobenzene did not affect neonates' weight, litter size, or viability during the pre-weaning period in any generation. In addition, there were no treatment-related effects on locomotor activity in the F1 or F2 generation rats. Of the organs weighed in the pups (liver, lungs, heart, kidneys, adrenals, and gonads, as well as seminal vesicles in males), only the adrenals were affected by 1,2,4-trichlorobenzene. Absolute weight of the adrenals of high-dose F0 and F1 males and females were significantly increased relative to controls (7–12%), although with no clear dose-response relationship. Microscopic examination of liver and kidneys from F1 rats showed no histological damage. Results from blood chemistry tests in F0 and F1 rats did not reveal any treatment-related alterations. The dose levels of 1,2,4-trichlorobenzene at which the increase in adrenal weight were observed in F0 males and females were estimated by the investigators to be 33 and 53.6 mg/kg/day, respectively.

NOAELs and LOAELs for developmental effects are presented in Tables 3-3, 3-4, and 3-5 and are plotted in Figure 3-3, 3-4, and 3-5.

3.2.2.7 Cancer

Two long-term bioassays are available for 1,2,4-trichlorobenzene. Groups of F-344 rats (50/sex/group) were fed a diet containing 0, 100, 350, or 1,200 ppm 1,2,4-trichlorobenzene for 104 weeks (Moore 1994a). The diet provided doses of 0, 5.6, 19.4, or 66.5 mg/kg/day to males and 0, 6.9, 23.5, or 81.4 mg/kg/day to females. In the study in mice, groups of B6C3F₁ mice (50/sex/group) were fed a diet containing 0, 150, 700, or 3,200 ppm 1,2,4-trichlorobenzene (98.9% pure) for 104 weeks (Moore 1994b). The diet provided doses of 0, 21, 100.6, or 519.9 mg/kg/day to males and 0, 26.3, 127, or 572.6 mg/kg/day to females. Parameters evaluated in both studies included mortality (twice daily), clinical signs, body weight, and food consumption (weekly for 16 weeks and every 4 weeks thereafter),

3. HEALTH EFFECTS

hematology (week 52 and 78 for cellular morphology and leukocyte differential, from control and high-dose groups), organ weight (at termination, brain, brainstem, liver, kidneys, testes, and epididymis), and necropsy and histopathology findings (at termination, all major organs and tissues).

There was no evidence of treatment-related increases in the incidences of neoplasia in rats. In mice, treatment with 1,2,4-trichlorobenzene resulted in significant early mortality in both high-dose male and female groups. Percent survival on week 105 was 90, 88, 82, and 10% in males and 78, 76, 84, and 0% in females from the control, low-, mid-, and high-dose mice, respectively. Histological examination of tissue and organs from both unscheduled deaths and terminal sacrifice showed significantly increased incidence of hepatocellular carcinoma in mid- and high-dose groups (males: 8/50, 5/50, 27/50, and 50/50; females: 1/50, 1/50, 28/50, and 46/50). Neoplasms in other organs showed comparable incidences between the control and treated groups.

EPA classified 1,2,4-trichlorobenzene in Group D: not classifiable as to human carcinogenicity (IRIS 2010), or as a chemical for which there is “Inadequate Information to Assess Carcinogenic Potential” according to the Guidelines for Carcinogen Risk Assessment (EPA 2005a). EPA’s classification was done in 1988 and was last revised in 1991.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to trichlorobenzenes.

A dermal LD₅₀ of 6,139 mg/kg was reported for 1,2,4-trichlorobenzene in Sprague-Dawley rats (Brown et al. 1969). This value is presented in Table 3-6. The investigators noted that low doses caused depression of activity, whereas lethal doses induced extensor convulsions, and that all deaths occurred within 5 days of exposure. Dermal LD₅₀ values of 300 and 305 mg/kg were estimated for 1,2,4-trichlorobenzene in mice applied doses ranging from 122 to 769 mg/kg (Yamamoto et al. 1978). During the 7-day observation period, no deaths occurred in the group dosed with 122 mg/kg 1,2,4-trichlorobenzene. No information was located regarding 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene.

Application of 0.5 mL of undiluted 1,2,4-trichlorobenzene to a shaven area of the back of guinea pigs 6 hours/day, 5 days/week for 3 weeks resulted in the death of an unspecified number of guinea pigs; the time of death was also not specified (Brown et al. 1969).

3. HEALTH EFFECTS

3.2.3.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each study for systemic effects in each species and duration category are recorded in Tables 3-6, 3-7, and 3-8.

No studies were located regarding systemic effects in humans after dermal exposure to trichlorobenzenes.

Respiratory Effects. Application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin of rabbits in doses of up to 450 mg/kg 5 days/week for 4 weeks did not induce histological alterations in the respiratory tract including the nasal turbinates (Rao et al. 1982).

Cardiovascular Effects. No histological alterations were observed in the heart from rabbits administered 0.2 mL of a 100% solution of technical-grade 1,2,4-trichlorobenzene (97 mg/kg) to the ear 3 times/week for 13 weeks (Powers et al. 1975). Similar results were reported in rabbits following application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks (Rao et al. 1982).

Gastrointestinal Effects. Application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin of rabbits in doses of up to 450 mg/kg 5 days/week for 4 weeks did not induce histological alterations in the gastrointestinal tract, including the nasal turbinates (Rao et al. 1982).

Hematological Effects. No treatment-related hematological alterations were reported in rabbits following application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks (Rao et al. 1982).

Musculoskeletal Effects. Histological examination of skeletal and bone from rabbits administered technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks did not show treatment-related effects (Rao et al. 1982).

Hepatic Effects. In an acute lethality study in mice applied single doses of 1,2,4-trichlorobenzene ranging from 123 to 769 mg/kg onto the skin, mice that survived the highest dose showed congestion and necrosis of the liver (Yamamoto et al. 1978). Guinea pigs that died following application of 0.5 mL of

Table 3-6 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Dermal

Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
ACUTE EXPOSURE							
Death							
Rat (Sprague-Dawley)	once (NS)			6139 B mg/kg	(LD50)	Brown et al.1969 1,2,4-trichlorobenzene	
Mouse (CD-1)	once			300 M mg/kg	(LD50)	Yamamoto et al. 1978 1,2,4-trichlorobenzene	
				305 F mg/kg	(LD50)		
Systemic							
Mouse (CD-1)	once	Hepatic	591 B mg/kg	769 B mg/kg	(liver congestion and necrosis)	Yamamoto et al. 1978 1,2,4-trichlorobenzene	
Mouse (CD-1)	once	Dermal		70 B %volume	(erythema)	Yamamoto et al. 1978 1,2,4-trichlorobenzene	
Gn Pig (albino)	3 wk	Dermal		0.05 M mL	(moderate to severe skin irritation in older guinea pigs)	E.I. Dupont 1971 1,2,4-trichlorobenzene	No to mild irritation was reported in young guinea pigs; TCB was 75% or 95% v/v
Rabbit (NS)	3 d 6 hr/d	Dermal		2 B mL	(spongiosis, acanthosis, parakeratosis)	Brown et al.1969 1,2,4-trichlorobenzene	

Table 3-6 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Dermal

(continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
			NOAEL	Less Serious		
Immuno/ Lymphoret						
Gn Pig (albino)	3 wk		0.05 M mL		E.I. Dupont 1971 1,2,4-trichlorobenzene	NOAEL is for skin sensitization; applied TCB was 95% solution
INTERMEDIATE EXPOSURE						
Death						
Gn Pig (NS)	3 wk 5 d/wk 1 x/d 6 hr/d			0.5 B mL/day	(death of unspecified number of g. pigs) Brown et al. 1969 1,2,4-trichlorobenzene	Neither number of g. pigs that died nor time of death provided)
Systemic						
Gn Pig (NS)	3 wk 5 d/wk 1 x/d 6 hr/d	Hepatic		0.5 B mL/day	(necrotic foci in the liver) Brown et al. 1969 1,2,4-trichlorobenzene	
		Dermal		0.5 B mL/day	(spongiosis, acanthosis, parakeratosis)	
Rabbit (NS)	3 wk 5 d/wk 1 x/d 6 hr/d	Dermal		1 B mL/day	(spongiosis, acanthosis, parakeratosis) Brown et al. 1969 1,2,4-trichlorobenzene	

Table 3-6 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Dermal

(continued)

Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Rabbit (New Zealand)	13 wk 3 x/wk	Cardio	97 B mg/kg			Powers et al. 1975 1,2,4-trichlorobenzene	Effects increased in severity as the dose increased to 97 mg/kg
		Hepatic	97 B mg/kg				
		Renal	97 B mg/kg				
		Dermal		4.8 B mg/kg	(slight skin redness and scaling with desquamation)		
		Bd Wt	97 B mg/kg				

Table 3-6 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Dermal

(continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
			NOAEL	Less Serious			Serious
Rabbit (New Zealand)	4 wk 5 d/wk 1 x/d	Resp	450 B mg/kg			Rao et al. 1982 1,2,4-trichlorobenzene NOAELs are for histopathology or organs and tissues	
		Cardio	450 B mg/kg				
		Gastro	450 B mg/kg				
		Hemato	450 B mg/kg				
		Musc/skel	450 B mg/kg				
		Hepatic	450 B mg/kg				
		Renal	450 B mg/kg				
		Endocr	450 B mg/kg				
		Dermal		30 B mg/kg	(slight gross and histological damage at application site)		
		Ocular	450 B mg/kg				
Bd Wt	450 B mg/kg						

Table 3-6 Levels of Significant Exposure to 1,2,4-Trichlorobenzene - Dermal

(continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
			NOAEL	Less Serious		
Immuno/ Lymphoret						
Gn Pig (NS)	3 wk 3 d/wk		0.1 %volume		Brown et al. 1969 1,2,4-trichlorobenzene	No skin sensitization was observed
Rabbit (New Zealand)	13 wk 3 x/wk		97 B mg/kg		Powers et al. 1975 1,2,4-trichlorobenzene	NOAEL is for gross and microscopic alterations in the spleen
Rabbit (New Zealand)	4 wk 5 d/wk 1 x/d		450 B mg/kg		Rao et al. 1982 1,2,4-trichlorobenzene	NOAEL is for histopathology of lymphoreticular organs
Reproductive						
Rabbit (New Zealand)	4 wk 5 d/wk 1 x/d		450 B mg/kg		Rao et al. 1982 1,2,4-trichlorobenzene	NOAELs are for histopathology or organs and tissues
CHRONIC EXPOSURE						
Systemic						
Mouse (CD-1)	104 wk 2 x/wk	Dermal		30 B %volume	(keratinization of epidermis, inflammation)	Yamamoto et al. 1982 1,2,4-trichlorobenzene
		Bd Wt	60 B %volume			The applied amount was 0.03 mL

B = both; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Table 3-7 Levels of Significant Exposure to 1,2,3-Trichlorobenzene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
ACUTE EXPOSURE							
Systemic							
Rabbit (NS)	once	Ocular		10 %volume	(slight conjunctival irritation and trace of corneal injury)	Dow Chemical 1956 1,2,3-Trichlorobenzene	
Rabbit (NS)	7 d 1 x/d	Dermal		100 %volume	(slight reddening of the skin to slight exfoliation after 7 applications)	Dow Chemical 1956 1,2,3-Trichlorobenzene	

d = day(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; x = time(s)

Table 3-8 Levels of Significant Exposure to 1,3,5-Trichlorobenzene - Dermal

Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL	Less Serious	Serious		
ACUTE EXPOSURE							
Systemic							
Rabbit (New Zealand)	once	Dermal		500 mg	(mild skin irritation)	Jorgenson et al. 1976 1,3,5-Trichlorobenzene	
Rabbit (New Zealand)	once	Ocular		100 mg	(mild, transitory eye irritation)	Jorgenson et al. 1976 1,3,5-Trichlorobenzene	
Immuno/ Lymphoret							
Gn Pig (Hartley)	once		0.1 M %volume			Jorgenson et al. 1976 1,3,5-Trichlorobenzene	No skin sensitization was observed.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

3. HEALTH EFFECTS

undiluted 1,2,4-trichlorobenzene to a shaven area of the back for 6 hours/day, 5 days/week for 3 weeks showed necrotic foci in the liver (Brown et al. 1969).

No histological alterations were observed in the liver from rabbits administered 0.2 mL of a 100% solution of technical-grade 1,2,4-trichlorobenzene (97 mg/kg) to the ear 3 times/week for 13 weeks (Powers et al. 1975). Application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin of rabbits in doses of up to 450 mg/kg, 5 days/week for 4 weeks did not induce histological alterations in the liver; grossly, however, the liver of rabbits treated with 450 mg/kg did show slight pallor (Rao et al. 1982).

Renal Effects. No histological alterations were reported in the kidneys from rabbits applied 0.2 mL of a 100% solution of technical-grade 1,2,4-trichlorobenzene (97 mg/kg) to the ear 3 times/week for 13 weeks (Powers et al. 1975). No histological alterations were reported in the kidneys from rabbits following application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks (Rao et al. 1982). However, urinalysis revealed a slight but significant increase in urinary coproporphyrin in high-dose males on day 24 of the study, which was considered only a slight or questionable effect of treatment.

Endocrine Effects. Microscopic examination of the pituitary gland, pancreas, adrenal gland, and thyroid and parathyroid glands from rabbits administered technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks showed no significant treatment-related alterations (Rao et al. 1982).

Dermal Effects. Application of 1,2,4-trichlorobenzene in concentrations of 70–100% to the skin of mice produced erythema, but histological examination of the skin showed no remarkable change (Yamamoto et al. 1978). Application of 0.05 mL of a 75% solution of 1,2,4-trichlorobenzene to the shaved intact shoulder of guinea pigs for 24 hours produced no to mild irritation in young animals, but moderate to severe irritation in older guinea pigs (E.I. DuPont 1971). In a repeated treatment study, 1 mL of undiluted 1,2,4-trichlorobenzene was applied in a patch of lint to the shaved skin of rabbits for 6 hours during 3 consecutive days (Brown et al. 1969). Seven days after the first application, histological examination of the skin showed spongiosis, acanthosis, and parakeratosis.

Repeated applications of a 10% solution of 1,2,3-trichlorobenzene to the abraded belly of rabbits caused questionable irritation and edema that healed normally (Dow Chemical 1956). When the solution was

3. HEALTH EFFECTS

applied to intact skin, essentially no response was observed except for slight exfoliation after six applications. Application of undiluted 1,2,3-trichlorobenzene to the intact skin induced slight reddening to slight exfoliation after seven applications. However, in the abraded area, the undiluted chemical produced moderate reddening of the skin, slight edema, and trace of necrosis; healing was described as ordinary (Dow Chemical 1956).

In a study with 1,3,5-trichlorobenzene, 500 mg of the chemical was applied to the abraded or intact skin of six rabbits (Jorgenson et al. 1976). The test sites were covered and 24 hours later, the excess compound was removed and the sites were scored for erythema and edema. All treated rabbits showed erythema and edema at the 24-hour reading, and only three rabbits showed erythema at the 72-hour reading. The chemical was considered mildly irritating.

Intermittent application of 0.5 mL of undiluted 1,2,4-trichlorobenzene to guinea pigs or 1 mL to rabbits for 3 weeks produced spongiosis, acanthosis, and parakeratosis in both species (Brown et al. 1969). Rabbits applied 0.2 mL of a 5% solution of technical-grade 1,2,4-trichlorobenzene (4.8 mg/kg) onto the ventral surface of the ear 3 times/week for 13 weeks showed slight redness with slight scaling and desquamation that did not increase in severity after 39 exposures (Powers et al. 1975). Rabbits applied 25 or 100% solutions (24 or 97 mg/kg) showed moderate to severe irritation characterized by slight to severe erythema, severe scaling, desquamation and encrustation with slight enlargement of the follicles, some hair loss, and scarring. There was no evidence of acne form dermatitis.

A study was conducted in rabbits in which the animals were applied technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of 0, 30, 150, or 450 mg/kg, 5 days/week for 4 weeks (Rao et al. 1982). At termination, the skin of all treated rabbits showed localized effects considered slight at the low- and mid-dose levels and moderate at the high-dose level. The effects consisted of an area where regrowing fur was matted by a white bran-like scale, slight thickening of the skin, fissures which progressed to erosions and shallow ulcers, and erythema. Increasing dose increased the affected area. Microscopically, the skin site showed changes including inflammation, focal erosion and ulcers, and accumulation of inflammatory cells with varying degrees of exudation. Some rabbits showed slight superficial edema with slight fibrosis.

Painting 0.03 mL of a 30% solution of 1,2,4-trichlorobenzene 2 times/week for 2 years induced thickening and keratinization of the epidermis followed by inflammation (Yamamoto et al. 1982).

3. HEALTH EFFECTS

Ocular Effects. Instillation of a 10% solution of 1,2,3-trichlorobenzene to the eyes of rabbits followed by washing with water produced marked pain, slight conjunctival irritation, and trace of corneal injury (Dow Chemical 1956). The corneal injury almost completely healed in 24 hours, and irritation almost completely healed in 48 hours. In the unwashed eye, there was marked pain, conjunctival irritation and no corneal injury; complete healing occurred in 24 hours. In unwashed eyes instilled with undiluted 1,2,3-trichlorobenzene, there was a trace of pain, slight conjunctival irritation, and no corneal injury; healing occurred in 48 hours. The same was found in the washed eye, but healing occurred in 24 hours.

In a study with 1,3,5-trichlorobenzene, an amount of 100 mg of the chemical was applied into the eyes of rabbits (Jorgenson et al. 1976). Some rabbits had the compound washed out at 30 seconds or 5 minutes after application, or did not have the compound washed out. The eye was graded for ocular lesions at 24, 48, 72, and 96 hours. There was no corneal damage in rabbits that underwent washing, but minor damage was observed in the no-wash group. The cornea returned to normal within 3 days. Occasional circumcorneal injection was seen in some rabbits, but all effects on the iris disappeared by posttreatment day 4. Conjunctival responses occurred in all treated rabbits and generally involved varying degrees of redness, chemosis, and discharge. The eyes of the rabbits in the 30-second wash group returned to normal within 24 hours, but the 5-minute wash group was not normal until day 3, and the no-wash group did not return to normal until day 7. The investigators concluded that 1,3,5-trichlorobenzene produced mild transitory eye irritation.

Histological examination of the eyes from rabbits administered technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks showed no significant treatment-related alterations (Rao et al. 1982).

Body Weight Effects. Application of 0.2 mL of a 100% solution of technical-grade 1,2,4-trichlorobenzene (97 mg/kg) to the ear of rabbits 3 times/week for 13 weeks did not affect body weight (Powers et al. 1975). Application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin of rabbits in doses of up to 450 mg/kg, 5 days/week for 4 weeks did not significantly affect body weight (Rao et al. 1982).

3.2.3.3 Immunological and Lymphoreticular Effects

No histological alterations were reported in the spleen from rabbits administered 0.2 mL of a 100% solution of technical-grade 1,2,4-trichlorobenzene (97 mg/kg) to the ear 3 times/week for 13 weeks

3. HEALTH EFFECTS

(Powers et al. 1975). Similar results were reported for the spleen, thymus, and lymph nodes from rabbits following application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks (Rao et al. 1982).

Tests for skin sensitization conducted with 1,2,4-trichlorobenzene or 1,3,5-trichlorobenzene in guinea pigs were negative (Brown et al. 1969; E.I. DuPont 1971; Jorgenson et al. 1976).

3.2.3.4 Neurological Effects

Microscopic examination of the brain, spinal cord, and peripheral nerve from rabbits applied technical-grade 1,2,4-trichlorobenzene onto a shaved area of the back skin in doses of up to 450 mg/kg, 5 days/week for 4 weeks showed no significant treatment-related alterations (Rao et al. 1982).

3.2.3.5 Reproductive Effects

Application of technical-grade 1,2,4-trichlorobenzene to a shaved area of the back skin of male and female rabbits in doses of up to 450 mg/kg, 5 days/week for 4 weeks did not induce gross or microscopic alterations in the reproductive organs (Rao et al. 1982).

3.2.3.6 Developmental Effects

No studies were located that assessed developmental effects in humans or animals following dermal exposure to trichlorobenzenes.

3.2.3.7 Cancer

A 2-year cancer study was conducted with 1,2,4-trichlorobenzene in mice (Yamamoto et al. 1982). Groups of Slc:ddY mice (75/sex/group) were painted with 0.03 mL of a 30 or 60% solution of 1,2,4-trichlorobenzene 2 times/week for 104 weeks. There was high mortality both in the treated and control groups, beginning on week 30. At week 83, <10% of treated females and <15% of treated males survived. The main causes of death were respiratory infections, amyloidosis, and tumors. Histological alterations in tissues appeared more prevalent in the high-dose group, but the number of mice examined was not indicated. Tumors developed in the lungs, kidneys, stomach, urinary bladder, mammary gland, and skin in both treated and control groups. There was no indication of the time to first tumor appearance or whether the tumors were all found in different animals or were multiple tumors in the same animal.

3. HEALTH EFFECTS

Skin tumors were classified as squamous cell carcinoma, papilloma, and fibroma. This study is inadequate for assessing the potential carcinogenicity of 1,2,4-trichlorobenzene following dermal exposure.

3.3 GENOTOXICITY

For the most part, genotoxicity data for trichlorobenzenes have provided negative evidence of mutagenicity in *in vitro* tests with prokaryotic organisms (i.e., *Salmonella typhimurium*) and positive evidence of deoxyribonucleic acid (DNA) damage at concentrations that were generally also cytotoxic in mammalian cell systems *in vitro*. *In vivo* studies suggest that trichlorobenzenes are clastogenic. The role, if any, that these effects may play in the liver carcinogenicity of 1,2,4-trichlorobenzene in mice (Moore 1994b) is unknown. Tables 3-9 and 3-10 provide a summary of genotoxicity data for these test systems.

In vitro Exposure Studies. As shown in Table 3-9, *in vitro* assays of gene mutation in various strains of *S. typhimurium* provided mostly negative results, regardless of the presence or absence of metabolic activation in the incubation medium (Ethyl Corp. 1975; Haworth et al. 1983; Jorgenson et al. 1976; Kubo et al. 2002; Lawlor et al. 1979; Nohmi et al. 1985; Ono et al. 1992; Schoeny et al. 1979).

Studies with mammalian cell systems *in vitro* assessed mainly clastogenicity, cytotoxicity, and DNA damage, and for the most part, yielded positive results. A series of experiments conducted by Fratello et al. (1997) showed 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene to induce DNA damage as assessed by detecting loss of DNA fragment by means of cytofluorimetric analysis. Since the preparations used (Chinese hamster V79 cells) were devoid of cytochrome P-450 activity, the DNA damage was attributed to the parent compound rather than to a toxic metabolite. 1,3,5-Trichlorobenzene was considerably less cytotoxic than the other two isomers (Fratello et al. 1997). A similar study also found 1,2,4-trichlorobenzene to be cytotoxic in Chinese hamster ovary cells by inhibiting protein and DNA synthesis (Garret and Lewtas 1983). 1,2,4-Trichlorobenzene produced positive results in tests for cytotoxicity in rat hepatocytes and was positive in a transformation assay in rat liver epithelial (ARL) cells in the absence of metabolic activation, but at concentrations that were toxic to the cells (Shimada et al. 1983). Conversely, in an hepatocyte primary culture (HPC)/DNA repair assay conducted by Shimada et al. (1983), 1,2,4-trichlorobenzene was not genotoxic to rat hepatocytes in the absence of metabolic activation.

3. HEALTH EFFECTS

Table 3-9. Genotoxicity of Trichlorobenzenes *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
<i>Salmonella typhimurium</i> , TA98, TA100, TA1535, TA1537	1,2,3-TCB	Gene mutation	–	–	Haworth et al. 1983
<i>S. typhimurium</i> , TA98, TA100	1,2,3-TCB	Gene mutation	–	–	Kubo et al. 2002
<i>S. typhimurium</i> , TA98, TA100, TA2637	1,2,3-TCB	Gene mutation	–	–	Nohmi et al. 1985
<i>S. typhimurium</i> , TA1535/pSK1002	1,2,3-TCB	Gene mutation	–	–	Ono et al. 1992
<i>S. typhimurium</i> , TA98, TA100, TA1535, TA1537	1,2,4-TCB	Gene mutation	–	–	Haworth et al. 1983
<i>S. typhimurium</i> , TA98, TA100	1,2,4-TCB	Gene mutation	–	–	Kubo et al. 2002
<i>S. typhimurium</i> , TA98, TA100, TA2637	1,2,4-TCB	Gene mutation	–	–	Nohmi et al. 1985
<i>S. typhimurium</i> , TA1535/pSK1002	1,2,4-TCB	Gene mutation	–	+	Ono et al. 1992
<i>S. typhimurium</i> , TA98, TA100, TA1535, TA1537	1,2,4-TCB	Gene mutation, microsomal assay	–	–	Schoeny et al. 1979
<i>S. typhimurium</i> , TA98, TA100, TA1535, TA1537, TA1538	1,2,4-TCB	Gene mutation	–	–	Ethyl Corp. 1975
<i>Saccharomyces cerevisiae</i> D3	1,2,4-TCB	Gene mutation, mitotic recombination assay	–	–	Ethyl Corp. 1975
<i>S. typhimurium</i> , TA98, TA100, TA1535, TA1537	1,3,5-TCB	Gene mutation	–	–	Haworth et al. 1983
<i>S. typhimurium</i> , TA98, TA100, TA2637	1,3,5-TCB	Gene mutation	–	–	Nohmi et al. 1985
<i>S. typhimurium</i> , TA1535/pSK1002	1,3,5-TCB	Gene mutation	–	–	Ono et al. 1992
<i>S. typhimurium</i> , TA98, TA100, TA1535, TA1537, TA1538	1,3,5-TCB	Gene Mutation	–	–	Jorgenson et al. 1976

3. HEALTH EFFECTS

Table 3-9. Genotoxicity of Trichlorobenzenes *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
<i>Escherichia coli</i> , WP2uvrA ⁻	1,3,5-TCB	Reverse gene mutation	–	–	Jorgenson et al. 1976
<i>E. coli</i> , W3110 and p3478	1,3,5-TCB	DNA repair assay	No data	–	Jorgenson et al. 1976
<i>Bacillus subtilis</i> , H17 and M45	1,3,5-TCB	DNA repair assay	No data	–	Jorgenson et al. 1976
<i>S. cerevisiae</i> D3	1,3,5-TCB	Mitotic recombination	(+)	(+)	Jorgenson et al. 1976
Mammalian cells:					
Chinese hamster lung (CHL) cells	1,2,3-TCB	Chromosomal aberrations	–	–	McElroy et al. 2003
Chinese hamster ovary (CHO) cells	1,2,3-TCB	Chromosomal aberrations	–	–	McElroy et al. 2003
Chinese hamster V79 cells	1,2,3-TCB	Cytotoxicity, neutral red uptake assay	No data	+	Fratello et al. 1997
Chinese hamster V79 cells	1,2,3-TCB	Cell replication (Colony forming ability)	No data	+	Fratello et al. 1997
Chinese hamster V79 cells	1,2,3-TCB	DNA damage	No data	+	Fratello et al. 1997
Chinese hamster V79 cells	1,2,4-TCB	Cytotoxicity, neutral red uptake assay	No data	+	Fratello et al. 1997
Chinese hamster V79 cells	1,2,4-TCB	Cell replication (Colony forming ability)	No data	+	Fratello et al. 1997
Chinese hamster V79 cells	1,2,4-TCB	DNA damage	No data	+	Fratello et al. 1997
CHO cells	1,2,4-TCB	Cytotoxicity	No data	+	Garrett and Lewtas 1983
Rat hepatocyte (male F344 Fischer)	1,2,4-TCB	Gene mutation, HPC/DNA repair assay	No data	–	Shimada et al. 1983
Rat hepatocyte (male F344 Fischer)	1,2,4-TCB	Cytotoxicity	No data	+	Shimada et al. 1983
Rat liver epithelial (ARL) cells (male F344 Fischer)	1,2,4-TCB	Gene mutation, Transformation Assay	No data	+	Shimada et al. 1983
Chinese hamster V79 cells	1,3,5-TCB	Cytotoxicity, neutral red uptake assay	No data	(+)	Fratello et al. 1997

3. HEALTH EFFECTS

Table 3-9. Genotoxicity of Trichlorobenzenes *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Chinese hamster V79 cells	1,3,5-TCB	Cell replication (Colony forming ability)	No data	(+)	Fratello et al. 1997
Chinese hamster V79 cells	1,3,5-TCB	DNA damage	No data	(+)	Fratello et al. 1997

+ = positive result; (+) = weakly positive result; — = negative result; DNA = deoxyribonucleic acid; HPC = hepatocyte primary culture; TCB = trichlorobenzene

3. HEALTH EFFECTS

Table 3-10. Genotoxicity of Trichlorobenzenes *In Vivo*

Species (test system)	Compound	End point	Results	Reference
Mouse (male NMR, 5/dose)	1,2,3-TCB	Chromosomal aberrations, micronucleus assay	+	Mohtashamipur et al. 1987
Mouse (male Swiss CD-1)	1,2,3-TCB	Chromosomal aberrations, micronucleous assay	+	Parrini et al. 1990
Mouse (male NMR, 5/dose)	1,2,4-TCB	Chromosomal aberrations, micronucleus assay	+	Mohtashamipur et al. 1987
Mouse (male Swiss CD-1)	1,2,4-TCB	Chromosomal aberrations, micronucleous assay	+	Parrini et al. 1990
Mouse (male NMR, 5/dose)	1,3,5-TCB	Chromosomal aberrations, micronucleus assay	+	Mohtashamipur et al. 1987
Mouse (male Swiss CD-1)	1,3,5-TCB	Chromosomal aberrations, micronucleous assay	+	Parrini et al. 1990
<i>Drosophila melanogaster</i>	1,3,5-TCB	Gene mutation, sex-linked recessive lethal test	-	Zimmering et al. 1985

+ = positive result; - = negative result; TCB = trichlorobenzene

3. HEALTH EFFECTS

1,2,4-Trichlorobenzene did not induce chromosomal aberrations in Chinese hamster lung (CHL) or ovary (CHO) cells in assays conducted with and without metabolic activation (McElroy et al. 2003).

In vivo Exposure Studies. There were few studies available for review that examined the potential *in vivo* genotoxicity of trichlorobenzenes; however, as seen in Table 3-10, the results of the available studies were mostly positive. Intraperitoneal administration of either one of the trichlorobenzene isomers to male NMRI mice in doses ranging from 210 to 1,700 mg/kg resulted in dose-related increases in micronuclei in polychromatic erythrocytes of the femoral bone marrow 30 hours after the first of two injections (Mohtashampur et al. 1987). A similar study in male Swiss CD1 mice also reported increases in micronuclei frequency in the femoral bone marrow 6 hours after a second intraperitoneal injection of 500–650 mg/kg of either one of the trichlorobenzene isomers (Parrini et al. 1990). There were no significant differences among the trichlorobenzenes in either study. In a sex-linked recessive lethal test, 1,3,5-trichlorobenzene was negative for mutagenesis in *Drosophila melanogaster* (Zimmering et al. 1985).

3.4 TOXICOKINETICS

Results from studies of orally exposed animals indicate that trichlorobenzene isomers are rapidly and extensively absorbed, widely distributed, and quickly eliminated. Urinary excretion of radiolabeled 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene has illustrated that at least 50–80% of the administered radioactivity is absorbed and excreted in rats within 24 hours of dose administration. Urinary elimination of metabolites is the major route of elimination, with fecal elimination representing a minor pathway. In bile duct-cannulated rats, significant enterohepatic circulation of metabolites has been demonstrated. Results from rat studies indicate that, once absorbed, all three isomers are widely distributed throughout the body and are detectable in tissue within 0.5 hours of dosing. Tissues with the highest peak concentrations following oral administration included fat, skin, liver, kidneys, bladder, and the gastrointestinal tract. Identification of metabolites in urine, feces, and bile following exposure of rabbits, rats, and monkeys to the individual isomers indicates that the parent compounds are metabolized to phenolic compounds through arene oxide intermediates, which are conjugated to glutathione, glucuronic acid, or sulfates before elimination in the urine, feces, or bile. Some evidence is available suggesting that conjugation with glutathione predominates in rats, whereas glucuronidation predominates in monkeys. Enzymes involved in the proposed metabolic schemes for each isomer have not been definitively identified. However, the initial formation of arene oxides and phenols is likely to be catalyzed by

3. HEALTH EFFECTS

cytochrome P450 (CYP) oxygenases. The relevance of the animal toxicokinetic information for humans has not been established because, as indicated below, there are no human data.

Studies describing the absorption, distribution, metabolism, and elimination of 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene following oral exposure in humans, as well as inhalation and dermal exposure in humans and animals, are not available.

3.4.1 Absorption

No information was located regarding absorption of trichlorobenzenes in humans following any route of exposure.

3.4.1.1 Inhalation Exposure

Quantitative data on the absorption of trichlorobenzenes following inhalation exposure are not available for animals. However, indirect evidence that 1,2,4-trichlorobenzene is absorbed through inhalation can be inferred from minor liver effects in rats following inhalation exposure (Kociba et al. 1981).

3.4.1.2 Oral Exposure

Evidence from elimination studies in animals indicate that trichlorobenzene isomers are rapidly and extensively absorbed through the gastrointestinal tract in animals.

1,2,3-Trichlorobenzene. Radiolabeled 1,2,3-trichlorobenzene has been detected in both the urine and feces of rats following oral exposure. Specifically, 92% of administered radioactivity was eliminated through the urine and feces within 24 hours of administration of a single 10 mg/kg gavage dose of ¹⁴C-labeled 1,2,3-trichlorobenzene to male Sprague-Dawley rats (Chu et al. 1987). Overall excretion increased to 95% at 48 hours post ingestion. The percentage of the administered radioactivity in urine alone accounted for 56 and 59% of the total ingested dose at 24 and 48 hours, respectively. Therefore, assuming that none of the radioactivity excreted in the feces was absorbed, at least 59% of the administered dose was absorbed. These results are also consistent with as much as 95% of the administered dose may have been absorbed if all radiolabeled material excreted in the feces had first been absorbed and excreted through the biliary system.

3. HEALTH EFFECTS

1,2,4-Trichlorobenzene. Within 7 days after receiving a dose of 50 mg/kg of ^{14}C -labeled 1,2,4-trichlorobenzene, male Wistar rats excreted 66 and 17% of the radioactivity in urine and feces, respectively, suggesting that at least 66% of the administered dose was absorbed (Tanaka et al. 1986). Radioactivity in expired air accounted for 2.1% of the absorbed dose. Excretion in all three excreta reached a peak on day 3, indicating rapid absorption and elimination. Measurements of biliary excretion for 4 days in bile-cannulated rats showed that radioactivity in bile accounted for 45% of the administered dose (Tanaka et al. 1986). Bakke et al. (1992) reported that >60% of a 21 mg/kg dose of ^{14}C -1,2,4-trichlorobenzene was excreted in bile, while 21% was excreted in the urine of bile-cannulated male Sprague-Dawley rats within 24 hours. Findings from this study indicate an 81% absorption rate following oral exposure to 1,2,4-trichlorobenzene. In control non-cannulated rats, 70 and 9% of the radioactivity was excreted within 24 hours in urine and feces, respectively (Bakke et al. 1992). Following 7 consecutive days of oral dosing of male Sprague-Dawley rats with 181.5 mg/kg/day ^{14}C -1,2,4-trichlorobenzene, radioactivity in urine was still detectable 21 days after the first oral administration; total radioactivity detected in urine accounted for approximately 72% of the administered dose (Smith and Carlson 1980). Radioactivity in the feces was not detectable past day 15 and accounted for only 4% of the administered dose. Thus, between 72 and 76% of the administered dose was absorbed in this study.

^{14}C -Labeled material was excreted by both monkeys and rats following oral exposure to a 10 mg/kg dose of ^{14}C -labeled 1,2,4-trichlorobenzene. By 24 hours after dosing, female Rhesus monkeys had excreted about 40% of the administered radioactivity in the urine and <1% in the feces. Male albino rats, however, excreted 84% of the administered radioactivity in the urine and 11% in the feces by 24 hours. With intravenous administration of 10 mg/kg ^{14}C -labeled 1,2,4-trichlorobenzene, monkeys eliminated about 22% of the administered radioactivity in urine within 24 hours (none was detected in feces), whereas radioactivity in 24-hour urine and feces in rats accounted for 78 and 7% of the administered dose, respectively (Lingg et al. 1982). These data suggest that differences in elimination rates between rats and monkeys may be due to species differences in metabolic rate or elimination rate, rather than absorption rate.

1,3,5-Trichlorobenzene. The excretion of radioactivity derived from 1,3,5-trichlorobenzene in both the urine and feces of rats has also been monitored following oral exposure. Within 24 hours of a single 10 mg/kg dose of ^{14}C -labeled 1,3,5-trichlorobenzene to male Sprague-Dawley rats, 82% of radioactivity was eliminated through the urine and feces (Chu et al. 1987). Overall excretion increased to 89% at 48 hours post ingestion. The percentage of administered radioactivity in urine accounted for 47 and 50% at 24 and 48 hours, respectively. Thus, assuming that none of the radioactivity excreted in the feces was

3. HEALTH EFFECTS

absorbed, at least 50% of the administered dose was absorbed. These results are also consistent with as much as 89% of the administered dose may have been absorbed if all radiolabeled material excreted in the feces had first been absorbed and excreted through the biliary system.

3.4.1.3 Dermal Exposure

No quantitative data were located on the absorption of trichlorobenzenes following dermal exposure of animals. Theoretical predictive models based on chemical and physical properties, however, have indicated that 1,2,4-trichlorobenzene has a significant potential for dermal absorption (Fiserova-Bergerova et al. 1990). Specifically, the findings of this study suggest that dermal exposure to 1,2,4-trichlorobenzene is expected to raise the biological levels of this isomer 30% above those occurring during inhalation exposure to threshold limit values. 1,2,4-Trichlorobenzene absorption can also be inferred from evidence of systemic toxicity in animals following dermal exposure (Brown et al. 1969; Yamamoto et al. 1978).

3.4.2 Distribution

1,2,3- and 1,3,5-Trichlorobenzene were detected in autopsies of Canadian citizens at median levels of 1.9 and 1.1 ng/g, respectively, and at maximum levels of 9.1 and 3.7 ng/g, respectively (Mes 1992). Levels were below the detection limits in blood samples. 1,2,4-Trichlorobenzene was detected in human follicular fluid at a mean concentration of 214 pg/mL for patients undergoing *in vitro* fertilization in Canada (Younglai et al. 2002). Trichlorobenzenes detected in the general population are the result of inhalation of ambient air and ingestion of food and drinking water contaminated with trichlorobenzenes. No specific information was located regarding distribution of trichlorobenzenes in children.

3.4.2.1 Inhalation Exposure

No data on the distribution of trichlorobenzenes following inhalation exposure were located for animals.

3.4.2.2 Oral Exposure

Trichlorobenzene isomers are readily distributed throughout bodily tissues in animals. However, the level of distribution and length of retention vary between isomers. Several studies have been conducted with ¹⁴C-labeled trichlorobenzenes. It should be noted that generally in these studies no distinction can be

3. HEALTH EFFECTS

made between parent compound, metabolites, and recycled carbon incorporated into body macromolecules.

1,2,3-Trichlorobenzene. Radioactivity was present in the blood and tissues of male Sprague-Dawley rats 0.5 hours following gavage administration of 10 mg/kg ¹⁴C-labeled 1,2,3-trichlorobenzene (Chu et al. 1987). Tissue concentrations peaked at 24 hours with very high concentrations appearing in the gastrointestinal tract (2,180 ppb), liver (277 ppb), fat (1,920 ppb), kidney (399 ppb), and bladder (284 ppb). Seven days after dosing, radioactivity in the brain, muscle, testes, and seminal vesicles were no longer detectable. Radioactivity was nearly undetectable in the liver, fat, and skin by 56 days after dosing (Chu et al. 1987). Chu et al. (1987) reported gas chromatography (GC) data that indicated that most of the radioactivity in skin, liver, and fat was the parent compound, whereas that in muscle and kidney was predominantly more polar metabolites.

1,2,4-Trichlorobenzene. Radioactivity was found in the blood and tissues of male Sprague-Dawley rats 0.5 hours after oral dosing with 10 mg/kg ¹⁴C-labeled 1,2,4-trichlorobenzene (Chu et al. 1987). Levels peaked around 4 hours and declined thereafter. High concentrations remained present in the bladder (1,280 ppb), kidney (1,160 ppb), fat (4,260 ppb), skin (243 ppb), liver (680 ppb), and adrenal glands (850 ppb) at 24 hours. Seven days after dosing, radioactivity was no longer detectable in the brain, spleen, muscle, testes, seminal vesicles, epididymis, or prostate. Most tissues showed levels of radioactivity barely distinguishable from background levels 28 days after dosing (<10 ppb except adrenals with 40 ppb) (Chu et al. 1987). Sprague-Dawley rats given a daily oral dose of 181.5 mg/kg ¹⁴C-labeled 1,2,4-trichlorobenzene for 7 consecutive days showed the highest initial concentration of radioactivity in the adrenal glands (Smith and Carlson 1980). This level declined rapidly and no radioactivity could be detected 11 days after dosing. Abdominal fat had the highest concentrations on day 1 (2,033 dpm/g) and maintained detectable concentrations (~20% of day 1 level) through the remainder of the 16-day observation period. The liver also maintained detectable concentrations (1,075 dpm/g on day 1 and 317 dpm/g on day 19) throughout the entire observation period (Smith and Carlson 1980). High levels of radioactivity were found in adipose tissue and skin (81 and 15% of administered dose, respectively) 12 hours following administration of a single 50 mg/kg oral dose of ¹⁴C-labeled 1,2,4-trichlorobenzene to male Wistar rats. Radioactivity was also detectable in muscle and intestine at this time (~8 and 5% of administered dose). By 168 days after dosing, radioactivity was virtually undetectable in all examined tissues (Tanaka et al. 1986).

3. HEALTH EFFECTS

1,3,5-Trichlorobenzene. An early study by Parke and Williams (1960) indicated a wide distribution of 1,3,5-trichlorobenzene following a 500 mg/kg dose in rabbits. Specifically, 13% of the administered dose was detected in the feces, 23% in the gut, 5% in the pelt, 5% in the depot fat, and 22% in the carcass 8 days after administration. A later study revealed radioactivity in the blood and tissues 0.5 hours after oral dosing of male Sprague-Dawley rats with 10 mg/kg of ¹⁴C-labeled 1,3,5-trichlorobenzene (Chu et al. 1987). As with the other isomers, levels of radioactivity peaked at 1 day after administration. The peak concentrations in tissues with the highest concentrations showed the following order: fat (8,960 ppb) > gastrointestinal tract > salivary gland > adrenal ≈ bladder > liver > kidney > pancreas > epididymis > prostate > skin > lung > seminal vesicle (410 ppb). Peak tissue concentrations were generally higher following administration of 1,3,5-trichlorobenzene compared with 1,2,3- and 1,2,4-trichlorobenzene (Chu et al. 1987). Chu et al. (1987) reported GC data that indicated that most of the radioactivity in skin, liver, and fat was the parent compound, whereas that in muscle and kidney was predominantly more polar metabolites. Côté et al. (1988) found an accumulation of trichlorobenzene isomers in the fat and liver of rats, indicating that 1,3,5-trichlorobenzene accumulated at a higher level in these tissues than 1,2,4- and 1,2,3-trichlorobenzene when presented at 1,000 ppm in food for 13 weeks. The levels of isomer in the fat (15.5–76 ppm in males; 7.8–49 ppm in females) were one order of magnitude higher than those found in the liver (1.4–4.3 ppm in males; 0.73–1.9 ppm in females).

Trichlorobenzenes have been identified in human breast milk; therefore, infants may also be potentially exposed through breast feeding (see Section 6.6, Exposures of Children).

3.4.2.3 Dermal Exposure

Quantitative data on the distribution of trichlorobenzenes following dermal exposure were not located for humans or animals.

3.4.3 Metabolism

There is no information regarding the metabolism of trichlorobenzenes in humans following exposure by any route or regarding the metabolism of trichlorobenzenes in animals following inhalation or dermal exposure. Several studies have examined and identified urinary metabolites following oral, intraperitoneal, or intravenous exposure of rabbits (Jondorf et al. 1955; Kohli et al. 1976; Parke and Williams 1960), rats (Bakke et al. 1992; Lingg et al. 1982), and monkeys (Lingg et al. 1982). Identified metabolites are consistent with the initial formation of phenolic intermediates (indicative of arene oxide intermediates), which become conjugated with glutathione or glucuronic acid prior to excretion in the

3. HEALTH EFFECTS

urine or bile. A comparison of rat and monkey urinary metabolites indicated that glutathione conjugation was the predominant pathway in rats, whereas glucuronidation was predominant in monkeys (Lingg et al. 1982). Figure 3-6 diagrams hypothesized metabolic pathways of trichlorobenzene isomers. To date, enzymes involved in the proposed steps have not been definitively established, but based on analogy to benzene and other halogenated benzenes, cytochrome P450 isozymes likely catalyze the initial formation of phenols through arene oxides.

1,2,3-Trichlorobenzene. Jondorf et al. (1955) identified urinary metabolites of all three isomers in Chinchilla rabbits given a single oral 500 mg/kg dose. Spectrophotometric analysis indicated that 1,2,3-trichlorobenzene was the most rapidly metabolized of the three isomers. This isomer was mostly metabolized to 2,3,4-trichlorophenol, but lesser amounts of 3,4,5-trichlorophenol and 3,4,5-trichlorocatechol were also detected. Of the administered dose, 62% was excreted in urine as oxygen conjugates containing glucuronic and sulphuric acids within 5 days. Major metabolite excretions rose to a maximum on the first day after dosing and were no longer detectable in rabbit urine after 5 days.

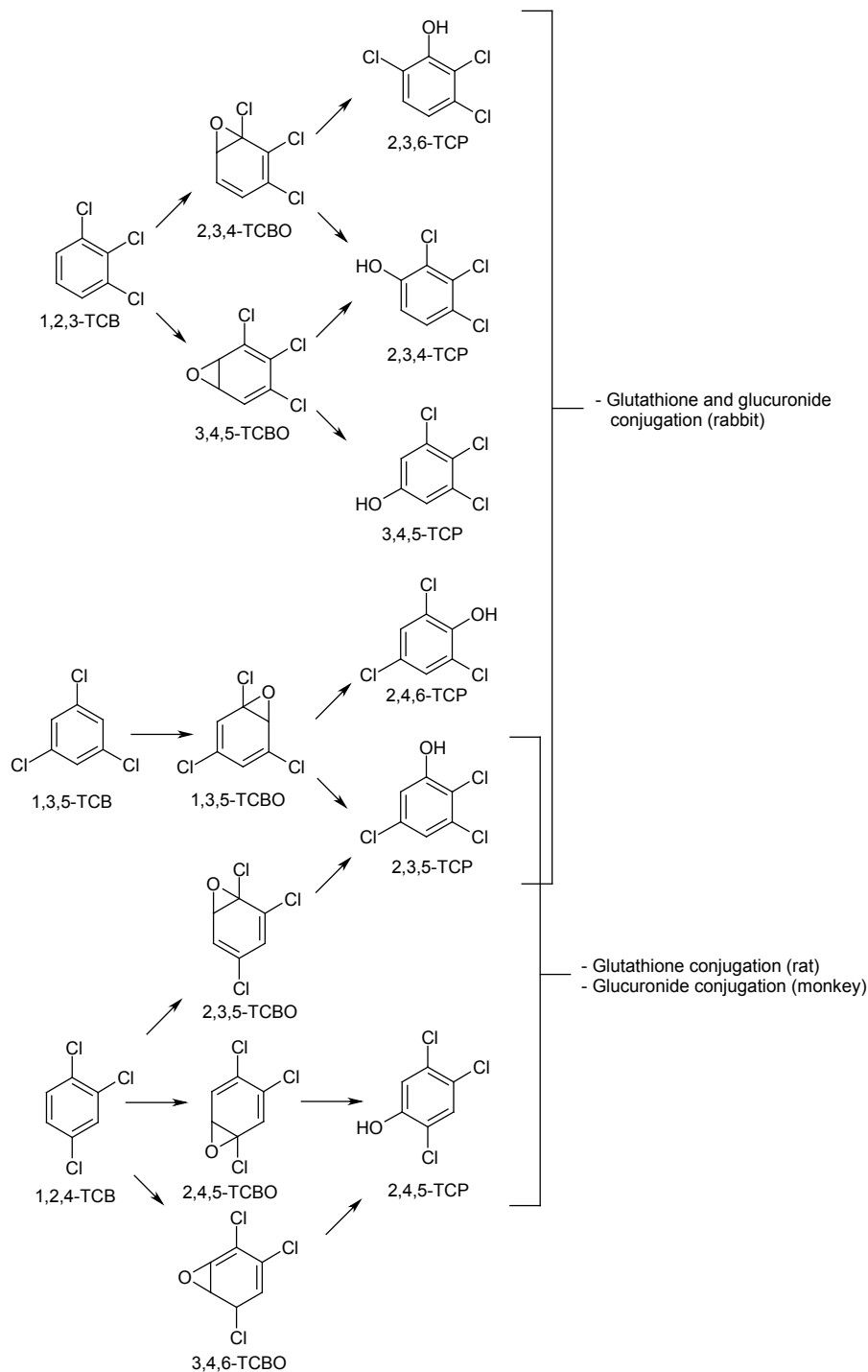
Kohli et al. (1976) identified urinary metabolites of trichlorobenzene isomers following a single 60–75 mg/kg intraperitoneal injection in male rabbits, finding similar results as those reported by Jondorf et al. (1955). Specifically, GC and mass spectrometry (MS) revealed the major metabolite of 1,2,3-trichlorobenzene to be 2,3,4-trichlorophenol with 2,3,6- and 3,4,5-trichlorophenol appearing at lower levels.

1,2,4-Trichlorobenzene. The only relevant information regarding metabolism of 1,2,4-trichlorobenzene in humans is that incubation of 1,2,4-trichlorobenzene with microsomes derived from cell lines expressing human CYP1A1, CYP1A2, CYP3A4, CYP2E1, and CYP2D6 showed that CYP2E1 had the highest enzymatic activity towards the chemical (Bogaards et al. 1995). The investigators also reported that in microsomal preparations from 22 human livers, CYP2E1 was the major enzyme involved in the formation of 2,3,5-trichlorophenol and 2,3,4-trichlorophenol from 1,2,4-trichlorobenzene, whereas CYP3A4 was responsible for the formation of 2,3,6-trichlorophenol.

In Chinchilla rabbits given a single 500 mg/kg dose by gavage, 1,2,4-trichlorobenzene was primarily metabolized to 2,4,5- and 2,3,5-trichlorophenol, with 5-day urinary metabolites of the isomer consisting of 38% glucuronic and sulphuric acid conjugates (Jondorf et al. 1955). Similar findings were obtained in a study examining urinary metabolites of trichlorobenzene isomers following a single 60–75 mg/kg intraperitoneal injection in male rabbits (Kohli et al. 1976). This study indicated that the primary

3. HEALTH EFFECTS

Figure 3-6. Hypothesized Metabolic Pathways for Trichlorobenzene Isomers Through Arene Oxide Intermediates



TCB = trichlorobenzene; TCBO = trichlorobenzene oxide; TCP = trichlorophenol

Source: Adapted from Kohli et al. (1976), with information from Bakke et al. (1992), Lingg et al. (1982), and Parke and Williams (1960).

3. HEALTH EFFECTS

metabolites of 1,2,4-trichlorobenzene were 2,3,5- and 2,4,5-trichlorophenol, while those of 1,3,5-trichlorobenzene were 2,3,5- and 2,4,6-trichlorophenol.

Further studies of 1,2,4-trichlorobenzene metabolism monitored urinary metabolites from rats and monkeys following oral or intravenous administration of single 10 mg/kg doses (Lingg et al. 1982). Although this study revealed similar metabolites as those previously observed in rabbits, some species-specific differences in conjugated metabolites were apparent. In rats, 60–62% of the urinary metabolites consisted of the mercapturic acids 2,3,5- and 2,4,5-*N*-acetyl-*S*-(trichlorophenyl)-*L*-cysteine 24 hours after dose administration. This finding suggests that conjugation with glutathione is the major metabolic pathway and that arene oxides, such as 3,4,6-trichlorobenzene oxide, are likely reactive metabolic intermediates in rats. In the urine of monkeys, isomeric glucuronides of 3,4,6-trichloro-3,5 cyclohexadiene accounted for between 48 and 61% of urinary metabolites. Sulfur-containing metabolites were not found in the urine of monkeys following oral dosing with 10 mg/kg, indicating that conjugation of metabolic intermediates to glucuronic acid, not glutathione conjugation, is important in the monkey.

A later study in bile-duct cannulated male Sprague-Dawley rats reported that over 60% of a 21 mg/kg oral dose of ¹⁴C-1,2,4-trichlorobenzene was excreted in bile, while 21 and 2% were excreted in the urine and feces, respectively, within 24 hours (Bakke et al. 1992). In intact rats, about 70 and 9% of the administered dose were excreted in the urine and feces, respectively, within 24 hours. In urine from cannulated rats, the major identified metabolites were consistent with catabolism following glutathione conjugation of phenolic intermediates. *S*-(trichlorophenyl)-*N*-(acetyl) cysteine was the major urinary metabolite identified; *S*-(dichloro-hydroxyphenol)-*N*-(acetyl) cysteine (another mercapturic acid), trichlorothiophenol, and trichlorophenol were present at lesser concentrations. Only trace levels of glucuronides and sulphate esters were detected. Bile showed a wider range of metabolites consistent with catabolism of glutathione conjugates and relatively more trichlorothiophenol compared with urine. A single 3.5 mg intraperitoneal injection of ¹⁴C-2,4,5-trichlorothiophenol resulted in excretion of 17% of the administered dose as *S*-glucuronide and 36% as *S*-(methylsulphonyl-dichlorophenyl)-mercapturic acid, metabolites not found in the excrement of rats dosed with 1,2,4-trichlorobenzene. These findings led to the suggestion that trichlorothiophenols are not major intermediates or end-products of enzymatic metabolism of trichlorobenzene in rats, but were formed from enterohepatic circulation via intestinal flora. This was later confirmed by Kato et al. (1993) who suggested that the formation of methylsulfonyl metabolites of 1,2,4-trichlorobenzene involves the initial biliary secretion of 1,2,4-trichlorobenzene metabolites into the intestinal tract, followed by metabolism by intestinal microflora and the absorption of secondary metabolites into the systemic circulation.

3. HEALTH EFFECTS

The metabolism of 1,2,4-trichlorobenzene *in vitro* has also been investigated. Incubation of 1,2,4-trichlorobenzene with liver microsomes from male rats pretreated with dexamethasone (DEX) showed the formation of trichlorohydroquinone in addition to various trichlorophenols (Den Besten et al. 1991). Trichlorohydroquinone, which appeared to be formed as a result of secondary metabolism, was found to covalently interact with microsomal protein. Both the conversion and the covalent binding of 1,2,4-trichlorobenzene were mediated by cytochrome P-450 as shown by the dependence on the presence of NADPH and the inhibitory action of metyrapone. The addition of glutathione reduced the covalent binding almost completely through the formation of water soluble conjugates. Pretreatment of the rats with different inducers resulted in preferential formation of different trichlorophenols. Induction with DEX resulted in preferential formation of 2,3,6-trichlorophenol, whereas other inducers preferentially produced 2,4,5-trichlorophenol. 2,4,6-Trichlorophenol was a minor metabolite in all microsomal suspensions, whereas 2,3,4-trichlorophenol and 2,3,5-trichlorophenol were formed only in trace amounts. Adding DNA to the microsomal suspension resulted in covalent binding of 1,2,4-trichlorophenol with the DNA, although to a much lesser extent than with proteins.

1,3,5-Trichlorobenzene. Following oral administration of a 500 mg/kg dose of 1,3,5-trichlorobenzene in Chinchilla rabbits, only one phenol was detected in the urine (2,4,6-trichlorophenol), and only 23% of the administered dose was excreted as conjugates of glucuronic and sulfuric acids within 5 days (Jondorf et al. 1955). A subsequent study by Parke and Williams (1960) further detailed the metabolism of 1,3,5-trichlorobenzene in Chinchilla rabbits given a single 500 mg/kg dose by gavage. Within the first 3 days after dosing, 2,4,6-trichlorophenol and some minor monochlorophenols were excreted in the urine. 2,4,6-Trichlorophenol continued to be excreted from days 4 through 9 with the addition of 4-chlorophenol elimination. The principal urinary metabolites identified in urine collected from male rabbits following an intraperitoneal injection of 300 mg 1,3,5-trichlorobenzene were 2,3,5- and 2,4,6-trichlorophenol (Kohli et al. 1976). A third more polar metabolite was identified, but insufficient material was available to determine the structure of the compound by MS.

3.4.4 Elimination and Excretion

No information was located regarding elimination and excretion of trichlorobenzenes in humans following any route of exposure.

3. HEALTH EFFECTS

3.4.4.1 Inhalation Exposure

No data were found on the elimination and excretion of trichlorobenzenes following inhalation exposure in animals.

3.4.4.2 Oral Exposure

All three isomers of trichlorobenzene have been shown to be rapidly and efficiently eliminated following oral exposure, principally via metabolites in the urine in rabbits (Jondorf et al. 1955) and rats (Bakke et al. 1992; Chu et al. 1987), although enterohepatic biliary circulation has been demonstrated in bile-cannulated rats (Bakke et al. 1992).

1,2,3-Trichlorobenzene. Jondorf et al. (1955) illustrated the rapid elimination of 1,2,3-trichlorobenzene in Chinchilla rabbits administered a 500 mg/kg oral dose. Five days after dosing, 78% of the administered dose had been excreted as trichlorophenols and 62% as oxygen conjugates in urine, with no trace of the isomer found in feces. In rats, 92% of ¹⁴C-labeled 1,2,3-trichlorobenzene was eliminated through the urine and feces within 24 hours of a single 10 mg/kg gavage dose (Chu et al. 1987). Overall excretion increased to 95% at 48 hours post ingestion. The percentage of the radiolabeled 1,2,3-isomer in urine alone accounted for 56 and 59% at 24 and 48 hours, respectively. Data for radioactivity in tissues measured at 0.5, 1, 2, and 4 hours and 1, 2, 7, 14, 28, and 56 days after dose administration were fit to a two-compartment elimination model; estimated half-lives were 9.2 and 145 hours for the first and second compartments, respectively.

1,2,4-Trichlorobenzene. Chinchilla rabbits excreted 42% of a single 500 mg/kg oral dose of 1,2,4-trichlorobenzene as trichlorophenols 5 days after administration (Jondorf et al. 1955). This same study also noted that 38% of the administered dose was excreted in the urine as oxygen conjugates during the same time frame. A later study in rats dosed with 50 mg/kg ¹⁴C-labeled 1,2,4-trichlorobenzene revealed 66 and 17% excretion of radioactivity in urine and feces, respectively, 7 days post administration (Tanaka et al. 1986). Radioactivity in expired air consisted of 2.1% of the absorbed dose. Excretion in all three excreta reached a peak on day 3. Biliary excretion accounted for 45% of the radioactivity. The authors considered the enterohepatic circulation of trichlorobenzene metabolites in the body as a possible explanation for the difference in biliary and fecal excretion rates. Bakke et al. (1992) reported that >60% of a 21 mg/kg dose of ¹⁴C-1,2,4-trichlorobenzene was excreted in bile, while 21% was excreted in the urine of bile-cannulated Sprague-Dawley rats within 24 hours. In control rats without bile cannulation,

3. HEALTH EFFECTS

70 and 9% of the administered radioactivity was excreted within 24 hours in the urine and feces, respectively (Bakke et al. 1992).

Following a longer period of exposure, 181.5 mg/kg/day of ^{14}C -labeled 1,2,4-trichlorobenzene for 7 consecutive days, Smith and Carlson (1980) found that the urinary and fecal excretion of the isomer-derived radioactivity in Sprague-Dawley rats peaked during the first 3 days of dosing and declined rapidly thereafter. Radioactivity in the feces was not detectable past day 15 and accounted for only 4% of the administered dose. Urinary excretion, however, displayed detectable radioactivity 21 days after the first oral administration. Radioactivity in the urine accounted for approximately 72% of the administered dose.

Showing variations between species, Lingg et al. (1982) measured excretion rates in both monkeys and rats given a 10 mg/kg oral dose of ^{14}C -labeled 1,2,4-trichlorobenzene. By 24 hours after dosing, monkeys had excreted 40% of the administered dose in the urine. Less than 1% was found in the feces. Rats excreted 84% of the oral dose via the urine by 24 hours; 11% was found in feces. Following intravenous administration of 10 mg/kg ^{14}C -labeled 1,2,4-trichlorobenzene, monkeys eliminated about 22% of the administered radioactivity in urine and none in the feces 24 hours after exposure. Rats, on the other hand, excreted 78 and 7% of the administered dose in urine and feces at 24 hours, respectively. Regardless of the route of exposure, rats excreted radioactivity at a rate roughly 2–3 times faster than monkeys following administration of ^{14}C -labeled 1,2,4-trichlorobenzene.

1,3,5-Trichlorobenzene. In Chinchilla rabbits dosed with a single 500 mg/kg dose by gavage, 9% of the administered dose was excreted as trichlorophenols in the urine during the 5 days after dosing (Jondorf et al. 1955), while 23% was excreted as oxygen conjugates. A follow-up study indicated that only 4 and 14% of a 500 mg/kg dose were eliminated as phenols 8 and 9 days after dosing, respectively (Parke and Williams 1960). A much higher level of excretion, 82% of ^{14}C -labeled 1,3,5-trichlorobenzene, was found in the urine and feces of Sprague-Dawley rats within 24 hours of a single 10-mg/kg gavage dose (Chu et al. 1987). Overall excretion increased to 89% at 48 hours post ingestion. The percentage of the radiolabeled 1,3,5-isomer in urine alone accounted for 47 and 50% at 24 and 48 hours, respectively. Data for radioactivity in tissues measured at 1, 2, 7, 14, 28, and 56 days after dose administration were fit to a two-compartment elimination model; estimated half-lives were 8 and 67.5 hours for the first and second compartments, respectively (Chu et al. 1987).

3. HEALTH EFFECTS

3.4.4.3 Dermal Exposure

No data on the elimination and excretion of trichlorobenzenes following dermal exposure were located for animals.

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

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

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.

3. HEALTH EFFECTS

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-7 shows a conceptualized representation of a PBPK model.

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

No PBPK/PD models have been developed for trichlorobenzenes.

3.5 MECHANISMS OF ACTION

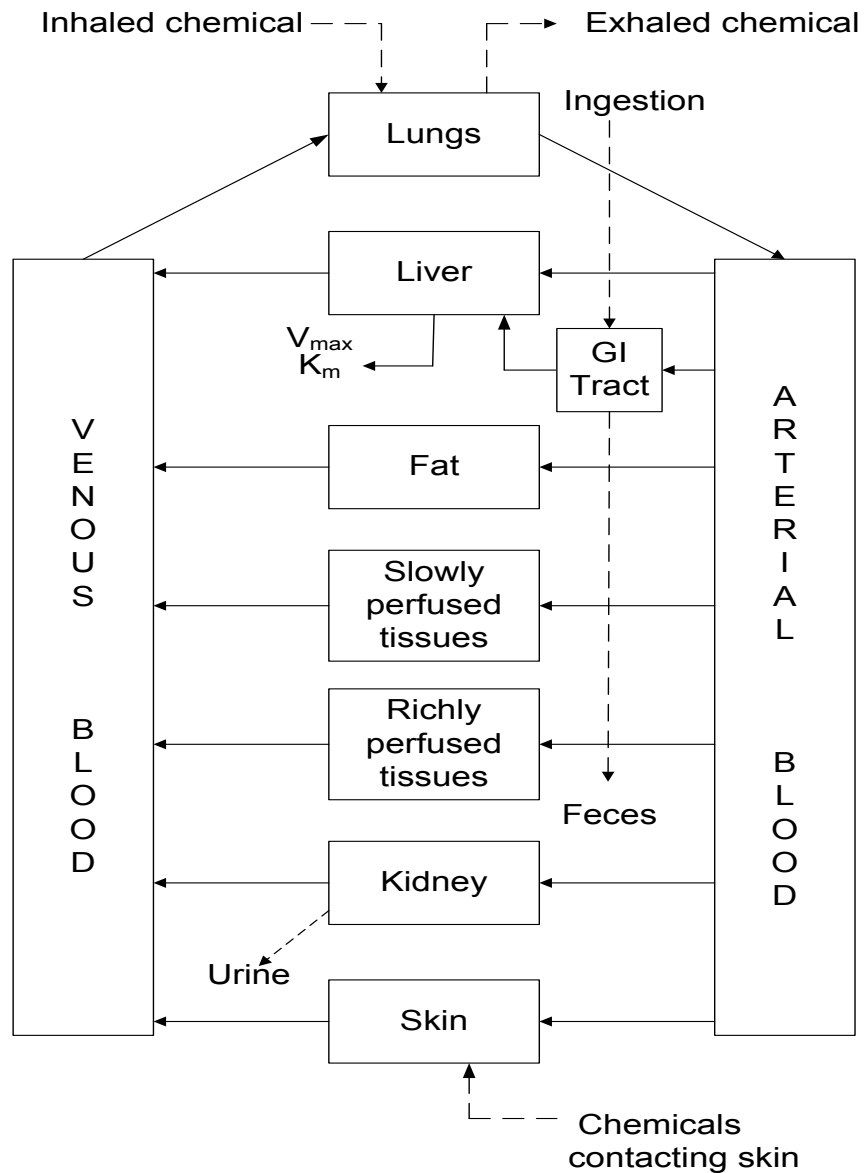
3.5.1 Pharmacokinetic Mechanisms

Studies in animals indicate that trichlorobenzenes are rapidly and efficiently absorbed through the gastrointestinal tract. However, the specific mechanisms by which this occurs have not been evaluated. Given that they are fairly soluble in lipids, it is reasonable to assume that absorption will occur through passive diffusion. No specific information was located regarding mechanisms of inhalation or dermal absorption. In addition, no relevant information was located regarding mechanisms of transport of trichlorobenzenes (or metabolites) in the blood, distribution to tissues, or storage in tissues.

The role of metabolism on the liver effects of 1,2,4-trichlorobenzene, specifically enzyme induction and alterations in heme metabolism, has been examined by Kato and coworkers (Kato and Kimura 2002; Kato et al. 1988, 1993). Intraperitoneal injection of the metabolite 2,3,5-trichlorophenyl methyl sulfone to

3. HEALTH EFFECTS

Figure 3-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

Source: adapted from Krishnan and Andersen 1994

3. HEALTH EFFECTS

male Wistar rats resulted in significant increases in the activities of aminopyrine N-demethylase and cytochrome P-450 content in liver microsomes, reaching a maximum at 48–72 hours after the injection (Kato et al. 1993). Significant increases in aniline hydroxylase and cytochrome b₅ contents were also observed at 12–120 hours and 24–120 hours, respectively. The rise and fall in enzyme activities correlated with the rise and fall of the hepatic concentration of 2,3,5-trichlorophenyl methyl sulfone rather than with the hepatic concentration of 1,2,4-trichlorobenzene. This was consistent with the estimated elimination half-lives from the liver of 5.2 hours and 37.8 hours for 1,2,4-trichlorobenzene and 2,3,5-trichlorophenyl methyl sulfone, respectively. In this study, 2,4,5-trichlorophenyl methyl sulfone was found to be a weaker inducer, although an earlier study had shown 2,4,5-trichlorophenyl methyl sulfone to induce a component of the microsomal electron transport system and also uridine diphosphate-glucuronyltransferase, a phase II metabolic enzyme (Kato et al. 1988). Overall, these findings strongly suggest that the inducing effect of 1,2,4-trichlorobenzene on liver microsomal drug-metabolizing enzymes is not due to the parent compound, but to its methanesulfonyl metabolite 2,4,5-trichlorophenyl methyl sulfone.

1,2,4-Trichlorobenzene has been shown to induce ALA synthetase, the rate-limiting enzyme in the biosynthesis of heme (Ariyoshi et al. 1975a, 1975b) and also heme oxygenase, the rate-limiting enzyme in the degradation of heme (Kato and Kimura 2002). Administration of 1,2,4-trichlorobenzene or 2,3,5-trichlorophenyl methyl sulfone to male Wistar rats resulted in significant increases in ALA synthetase activity, but only 1,2,4-trichlorobenzene induced heme oxygenase (Kato and Kimura 2002). In both cases, there were significant increases in the contents of cytochrome P-450, which paralleled increases in total heme content. In rats with reduced liver glutathione levels by pretreatment with buthionine-(*S,R*)-sulfoximine (BSO) and dosed with 1,2,4-trichlorobenzene, 2,3,5-trichlorophenyl methyl sulfone was present in the liver at much lower concentrations than in rats not pretreated with BSO. In addition, 1,2,4-trichlorobenzene did not induce ALA synthetase in BSO-treated rats, but 2,3,5-trichlorophenyl methyl sulfone did, suggesting that the induction of ALA synthetase in rats dosed with 1,2,4-trichlorobenzene is not due to 1,2,4-trichlorobenzene, but to 2,3,5-trichlorophenyl methyl sulfone. Kato and Kimura (2002) suggested that the prolonged induction of ALA synthetase by 2,3,5-trichlorophenyl methyl sulfone results in excess heme biosynthesis, which overrides the destruction of heme that results from the induction of heme oxygenase by 1,2,4-trichlorobenzene or a metabolite other than 2,3,5-trichlorophenyl methyl sulfone. This is consistent with the induction of porphyria in rats dosed with 1,2,4-trichlorobenzene (i.e., Rimington and Ziegler 1963).

3. HEALTH EFFECTS

No studies were located that examined the effect of dose on metabolism or excretion pathways of trichlorobenzenes.

3.5.2 Mechanisms of Toxicity

The toxicity of trichlorobenzenes does not appear to be route-dependent, and the liver appears to be the main target regardless of the duration of exposure.

The mechanism(s) of liver toxicity induced by trichlorobenzenes has not been elucidated, but it probably involves arene oxide intermediates which form during the initial transformation to trichlorophenols. As mentioned above, 1,2,4-trichlorobenzene, and presumably the other isomers, induce a number of drug-metabolizing enzymes in the liver of rats which will affect the biotransformation of other chemicals. Whether or not this will result in increased toxicity of other xenobiotics will depend on whether the toxicity of the other chemical is due to the parent compound or to a metabolite. Also, as mentioned above, exposure to 1,2,4-trichlorobenzene induced porphyria in rats by inducing ALA synthetase and thus increasing heme production. Trichlorobenzenes and other chlorinated benzenes induce nephropathy in the male rat by a mechanism that involves a series of events beginning with an excessive accumulation of hyaline droplets. This appears to be unique to the male rat and is not relevant for human risk assessment. A study of 1,2,4-trichlorobenzene with liver microsomes from male rats *in vitro* reported the formation of trichlorohydroquinone as a result of secondary metabolism (Den Besten et al. 1991). Trichlorohydroquinone was found to covalently interact with microsomal protein and with added DNA. Whether or not this plays a role in the *in vivo* toxicity of 1,2,4-trichlorobenzene is unknown.

3.5.3 Animal-to-Human Extrapolations

There is virtually no information on health effects of trichlorobenzenes in humans, so the animal species that is the most appropriate model for human exposure is not known. The liver is the target for trichlorobenzenes in animals, and rats appear to be more sensitive than other species. Based on information from effects of other chlorinated benzenes in humans, and from limited information on the metabolism of 1,2,4-trichlorobenzene by microsomal preparations from human livers that indicated that cytochrome P-450 enzymes might be involved in the metabolism of trichlorobenzenes, it is reasonable to suggest that excessive exposure to trichlorobenzenes might induce liver effects such as porphyria in humans.

3. HEALTH EFFECTS

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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

There is no evidence from the reproductive and developmental studies, summarized in Sections 3.2.2.5 and 3.2.2.6, respectively, that suggests that trichlorobenzenes affect the neuroendocrine axis.

3. HEALTH EFFECTS

The only relevant information that was located regarding *in vitro* tests is that 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene tested negative for estrogenic activity in a reporter gene expression assay using yeast cells (Nishihara et al. 2000). A substance was considered positive when its activity was more than 10% of the activity of 10^{-7} M 17β -estradiol.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at

3. HEALTH EFFECTS

this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or do they render it more vulnerable to toxic injury. Each case of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

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.

3. HEALTH EFFECTS

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

No studies were located that described health effects in children following exposure to trichlorobenzenes. Also, no studies were located that compared the health effects of these compounds in young and adult animals to ascertain potential age-related differences in susceptibility.

Standard developmental toxicity studies in animals do not suggest that trichlorobenzenes are embryotoxic or teratogenic or that they alter the development of young animals. The only effects reported in a study with 1,2,4-trichlorobenzene in rats were the presence of microscopic alterations in the lenses of the eye of fetuses from dams treated with 150 mg/kg/day 1,2,4-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22 (Black et al. 1988). However, no lesions were observed in fetuses from dams dosed with 300 mg/kg/day 1,2,4-trichlorobenzene. This lesion was also observed in fetuses from dams dosed with 150, 300, or 600 mg/kg/day 1,3,5-trichlorobenzene; however, since no quantitative data were presented, it is not known whether the incidences were dose-related. Another gestational exposure study reported retarded development of the fetuses from rats dosed with 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 and sacrificed on Gd 14 (Kitchin and Ebron 1983). This dose level was lethal to two out nine dams and induced significant weight loss in dams that survived, which may have contributed to the delayed development of the fetuses. In studies of pregnant mice dosed with 0 or 130 mg/kg/day 1,2,4-trichlorobenzene on Gd 8–12, the chemical did not affect pup's viability or growth, or offspring's locomotor activity or fertility to produce a second generation (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986).

Trichlorobenzenes have been identified in breast milk; therefore, infants may also be potentially exposed through breast feeding (see Section 6.6, Exposures of Children). No information was located regarding the pharmacokinetics of these compounds in children, regarding biomarkers of exposure or effect for these compounds in children, or regarding interactions with other chemicals in children.

3. HEALTH EFFECTS

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), 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 exposures 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 trichlorobenzenes are discussed in Section 3.8.1.

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

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

3. HEALTH EFFECTS

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Trichlorobenzenes

Trichlorobenzenes have been detected in blood (Bristol et al. 1982; Mes 1992; Pellizzari et al. 1985a), adipose tissue (Mes 1992), and exhaled breath (Pellizzari et al. 1985b) and their presence in the body can be used as biomarkers of exposure to trichlorobenzenes. However, metabolites of trichlorobenzenes, such as trichlorophenols, cannot be used as specific biomarkers for exposure to trichlorobenzenes because they can also be generated from the metabolism of other chlorinated compounds such as the pesticide lindane (Agency for Toxic Substances and Disease Registry 2005).

3.8.2 Biomarkers Used to Characterize Effects Caused by Trichlorobenzenes

No specific biomarker of effects could be identified from the very limited information regarding humans exposed to trichlorobenzenes (see Section 3.2.1.2, Systemic Effects). Based on the existing information regarding the effects of trichlorobenzenes in animals, it is difficult to envision a health condition that could be attributed solely to exposure to trichlorobenzenes.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding interactions among trichlorobenzenes and limited data were found regarding interactions between trichlorobenzenes and other chemicals. Since trichlorobenzenes are inducers of liver microsomal enzymes (Ariyoshi et al. 1975a, 1975b; Carlson and Tardiff 1976; Kato and Kimura 2002; Kato et al. 1988, 1993; Kitchin and Ebron 1983), they will affect the metabolism of other compounds. For example, gavage administration of 1,2,4-trichlorobenzene at 600 mg/kg/day to rats for 14 days significantly decreased hexobarbital sleeping time (Carlson and Tardiff 1976). In another study, 1,2,4-trichlorobenzene increased the LD₅₀ values for malathion, malaoxon, parathion, and paraoxon in mice (Townsend and Carlson 1981). In the same study, 1,2,4-trichlorobenzene protected against the decrease in brain cholinesterase induced by malathion, but not against reductions in liver, plasma, or RBC cholinesterase. The protection afforded by 1,2,4-trichlorobenzene correlated well with increased carboxylesterase activity. These examples can be considered inhibitory types of interactions.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to trichlorobenzenes than will most persons exposed to the same level of trichlorobenzenes in the environment. Reasons may include genetic

3. HEALTH EFFECTS

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of trichlorobenzenes, or compromised function of organs affected by trichlorobenzenes. Populations who are at greater risk due to their unusually high exposure to trichlorobenzenes are discussed in Section 6.7, Populations with Potentially High Exposures.

A specific target for trichlorobenzene toxicity in humans exposed to these compounds has not been identified, but it is reasonable to assume that the liver could be a main target based on studies in animals. Therefore, individuals with compromised liver function may represent a susceptible population. No information was located regarding whether or not children represent a group unusually susceptible to trichlorobenzenes.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to trichlorobenzenes. 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 trichlorobenzenes. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts were identified that provide specific information about treatment following exposures to trichlorobenzenes.

3.11.1 Reducing Peak Absorption Following Exposure

The following information has been extracted from HSDB (2010). Methods for reducing peak absorption of trichlorobenzenes include gut dilution with water or milk and eye irrigation with water or sterile saline. Activated charcoal is not recommended, as it may promote vomiting and make endoscopic evaluation difficult. If exposure occurs via the dermal route, contaminated clothing should be removed and affected areas should be washed with soap. Exposure to fresh air or oxygen treatment is recommended to reduce absorption after inhalation exposure to trichlorobenzenes.

3.11.2 Reducing Body Burden

No information was located regarding reducing body burden of trichlorobenzenes following exposure to these chemicals.

3. HEALTH EFFECTS

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Studies in animals indicate that isomers of trichlorobenzene enhance xenobiotic metabolism via the induction of numerous hepatic drug-metabolizing enzymes including cytochromes c and P-450, glucuronyltransferase, glutathione S-transferase, and microsomal proteins (Ariyoshi et al. 1975a, 1975b; Kato and Kimura 2002; Kato et al. 1988, 1993). Also induced by 1,2,4-trichlorobenzene is ALA synthetase, the rate-limiting enzyme in heme biosynthesis (Ariyoshi et al. 1975a, 1975b), which is the cause of hepatic porphyria in rats treated with 1,2,4-trichlorobenzene (Rimington and Ziegler 1963). Studies suggest that both the induction of hepatic microsomal drug-metabolizing enzymes and ALA synthetase may not be mediated directly by 1,2,4-trichlorobenzene, but by its metabolite 2,3,5-trichlorophenyl methyl sulfone (Kato and Kimura 2002; Kato et al. 1988, 1993). Since 2,3,5-trichlorophenyl methyl sulfone results from the conjugation of glutathione with a 1,2,4-trichlorobenzene hydroxyl derivative, theoretically, reducing glutathione levels would prevent, at least in part, the effects of 1,2,4-trichlorobenzene.

3.12 ADEQUACY OF THE DATABASE

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

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

3.12.1 Existing Information on Health Effects of Trichlorobenzenes

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzenes are summarized in Figures 3-8, 3-9, and 3-10, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of

3. HEALTH EFFECTS

Figure 3-8. Existing Information on Health Effects of 1,2,3-Trichlorobenzene

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

Human

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

Animal

● Existing Studies

3. HEALTH EFFECTS

Figure 3-9. Existing Information on Health Effects of 1,2,4-Trichlorobenzene

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

Human

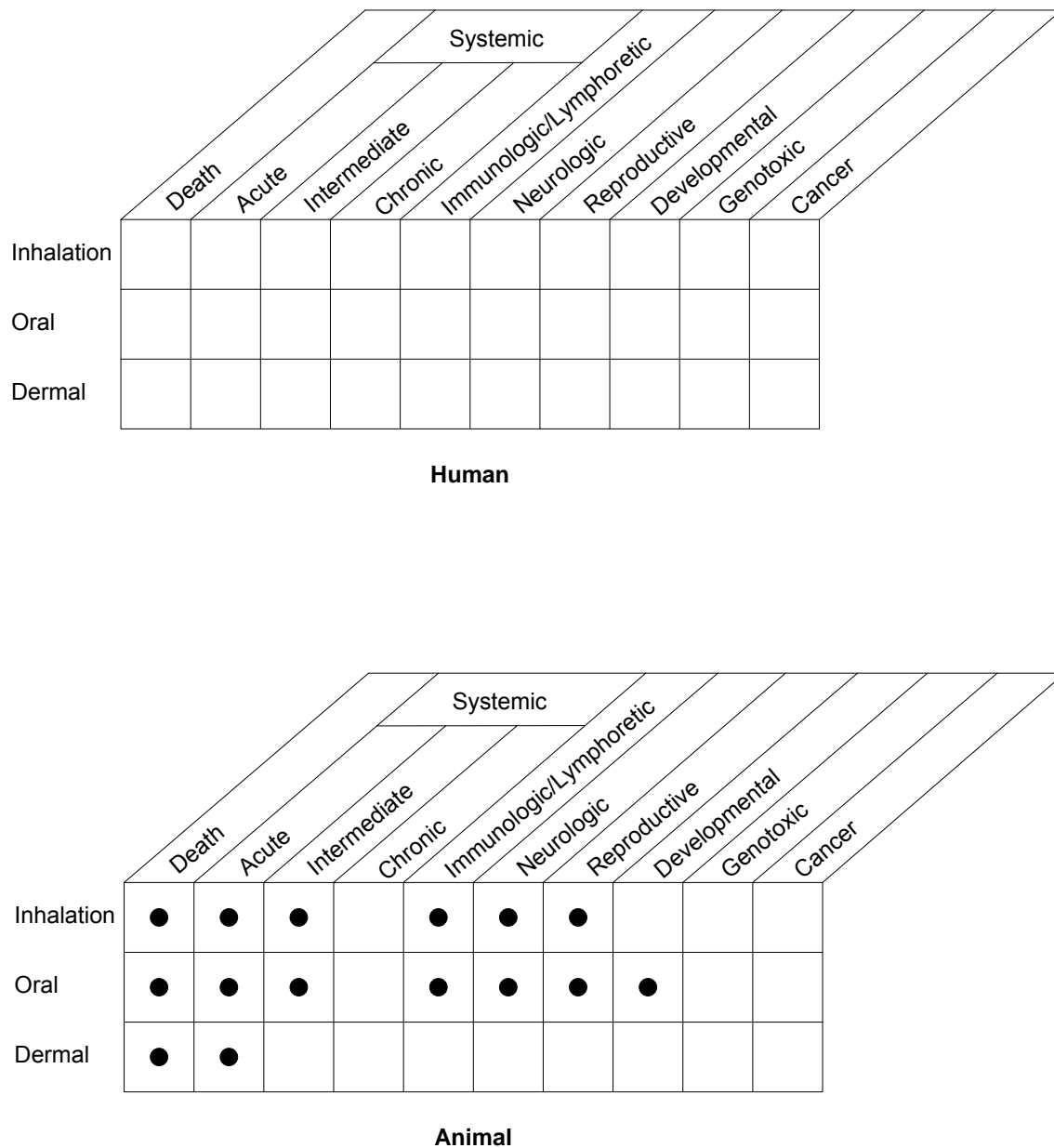
	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●	●		●	●	●			
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●	●		●	●	●			●

Animal

● Existing Studies

3. HEALTH EFFECTS

Figure 3-10. Existing Information on Health Effects of 1,3,5-Trichlorobenzene



● Existing Studies

3. HEALTH EFFECTS

trichlorobenzene. Each dot in the figures indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There is virtually no information regarding health effects in humans exposed to trichlorobenzenes. Information is available regarding health effects in animals exposed orally and dermally to each one of the three trichlorobenzene isomers and exposed by inhalation to 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene. 1,2,4-Trichlorobenzene has been the most widely studied of the three isomers. Chronic-duration studies in animals are available only for 1,2,4-trichlorobenzene and only via the oral route of exposure. Studies in animals showed that the liver is a target for trichlorobenzene toxicity, particularly in rats. The kidney was also affected in male rats, but this effect appears to be a unique response of male rats to exposure to a variety of organic chemicals and not relevant to humans. 1,2,4-Trichlorobenzene was evaluated for carcinogenicity in rats and mice; this isomer induced malignant liver tumors in mice. Trichlorobenzenes induced transitory skin and eye irritation when applied onto the skin or instilled into the eyes of animals.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No acute-duration studies were located in humans exposed by inhalation to trichlorobenzenes that could be used for derivation of an acute-duration MRL for this route. A review of the literature indicates that an adult male who inhaled trichlorobenzene for several hours during the repair of a pump suffered massive hemoptysis, and that some trichlorobenzene production workers developed chloroacne (IPCS 1991). Citing an unpublished source, ACGIH (2001) stated that minimal eye and throat irritation could occur in some people exposed to 3–5 ppm 1,2,4-trichlorobenzene. No relevant inhalation studies were located of animals exposed to 1,2,4-trichlorobenzene or 1,3,5-trichlorobenzene, and no information was located for 1,2,3-trichlorobenzene. A decision to conduct studies in animals for possible derivation of acute-duration inhalation MRLs for trichlorobenzenes has to be made after evaluating the likelihood that exposure to high concentrations of these chemicals for short periods of time will occur. No information was located regarding oral toxicity of trichlorobenzenes in humans. Aside from studies that provided information on lethal doses of trichlorobenzenes in animals (Brown et

3. HEALTH EFFECTS

al. 1969; Côté et al. 1988; Jorgenson et al. 1976), there are few studies available that examined the effects of acute oral exposure to these compounds. A developmental study in rats exposed to the three trichlorobenzene isomers during Gd 6–15 conducted histological evaluations of tissues and organs from the dams sacrificed on Gd 22 (Black et al. 1988). The liver and possibly the thyroid appeared to be targets for trichlorobenzenes; however, no quantitative data were presented, so NOAELs or LOAELs could not be defined and the study could not be used for MRL derivation. A 14-day gavage study with 1,2,4-trichlorobenzene in rats by Carlson and Tardiff (1976) identified the liver as a target for this isomer based on increases in liver weight and enzyme induction, but did not provide data regarding histopathology of the liver; therefore, it was considered inadequate for MRL derivation. While additional studies that provide adequate data for establishing dose-response relationships for acute exposure to the trichlorobenzenes would be valuable, particularly for liver effects, it is unlikely that acute oral exposure to high amounts of trichlorobenzenes will occur in humans. Studies in animals are available indicating that trichlorobenzenes are mild to moderate skin and eye irritants (Brown et al. 1969; Dow Chemical 1956; E.I. Dupont 1971; Jorgenson et al. 1976; Yamamoto et al. 1978). Additional acute-duration dermal studies do not seem necessary at this time.

Intermediate-Duration Exposure. No studies were located regarding health effects in humans exposed to trichlorobenzenes for intermediate duration periods by any route of exposure. Intermediate-duration inhalation studies in animals are available for 1,2,4-trichlorobenzene in various animal species (Coate et al. 1977; Gage 1970; Kociba et al. 1981) and for 1,3,5-trichlorobenzene in rats (Sasmore et al. 1983). The results showed that exposure to up to 100 ppm 1,2,4-trichlorobenzene for up to 26 weeks or 130 ppm 1,3,5-trichlorobenzene for 13 weeks had no significant effect on hematological and clinical chemistry tests or on histological appearance of tissues and organs. Although there is suggestive evidence from some studies that the liver might be a target for 1,2,4-trichlorobenzene, inadequacies in the studies (no quantitative data, too few animals) precluded derivation of an intermediate-duration inhalation MRL for this isomer. No intermediate-duration inhalation study for 1,2,3-trichlorobenzenes was located; however, there is no reason to believe that the results would have been different than those obtained for 1,2,4-trichlorobenzene or 1,3,5-trichlorobenzene. It should be noted that the exposure levels used in the animal studies are several orders of magnitude higher than those monitored in outdoor air in the United States in 2008 (EPA 2010a; see Section 6.4, Levels Monitored or Estimated in the Environment). Additional inhalation studies in animals do not seem necessary at this time. Wide-scope intermediate-duration oral studies in animals are available for 1,2,4-trichlorobenzene in rats (CMA 1989; Côté et al. 1988) and mice (Hiles 1989) and for 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene in rats (Côté et al. 1988). These studies identified the liver as the main target for trichlorobenzenes. Kidney effects were

3. HEALTH EFFECTS

also reported in male rats, but this response was characterized by hyaline droplet accumulation and was unique to the male and considered not relevant for human risk assessment. The studies by CMA (1989) in rats and Hiles (1989) in mice provided quantitative histological data, and the former was used to derive an intermediate-oral MRL for 1,2,4-trichlorobenzene. The study with 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene in rats (Côté et al. 1988) reported quantitative changes in liver weight and histological alterations in the liver and thyroid in treated groups of rats. However, quantitative histological data were not provided and, therefore, NOAELs and LOAELs for histological alterations could not be defined; thus, the study was considered inadequate for derivation of intermediate-duration oral MRLs for 1,2,3- and 1,3,5-trichlorobenzene. Additional studies that provide quantitative histological data would be valuable to define better points of departure for MRL derivation than organ weight. Intermediate-duration dermal studies are available for 1,2,4-trichlorobenzene (Brown et al. 1969; Powers et al. 1975; Rao et al. 1982). For the most part, effects were limited to the site of application of the chemical. Additional dermal studies with 1,2,4-trichlorobenzene do not seem necessary. Although no intermediate-dermal studies were located for 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene, it is unclear what key new information such studies would provide.

Chronic-Duration Exposure and Cancer. No studies were located regarding health effects in humans exposed chronically to trichlorobenzenes. Health evaluations of workers exposed to trichlorobenzenes may have been conducted, but none were identified in the literature reviewed. No chronic-duration inhalation animal studies are available for trichlorobenzenes. Since chlorobenzenes have been detected in outdoor air from cities in the United States (EPA 2010a), the general population is exposed to these chemicals by inhalation. However, as mentioned above, the exposure levels monitored in that study were several orders of magnitude lower than those used in intermediate-duration inhalation studies in animals which did not induce significant health effects. Therefore, the value of conducting chronic-duration inhalation studies with exposure concentrations around environmental levels is questionable. There are chronic-duration oral studies with 1,2,4-trichlorobenzene in rats (Moore 1994a) and mice (Moore 1994b). These studies reported adverse histological effects in the liver from rats and mice and also renal lesions in male rats. The liver effects in rats served as basis for the derivation of a chronic-duration oral MRL for 1,2,4-trichlorobenzene.

There are no studies of cancer in humans exposed to trichlorobenzenes. Both the chronic-duration oral study with 1,2,4-trichlorobenzene in rats (Moore 1994a) and mice (Moore 1994b) evaluated the animals for tumors and reported that 1,2,4-trichlorobenzene increased the incidence of hepatocellular carcinoma in both male and female mice. Additional cancer studies for this isomer do not appear necessary, but oral

3. HEALTH EFFECTS

toxicity/carcinogenicity studies for 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene seem warranted since the general population is exposed to these isomers through the consumption of fish and other foods (see Section 6.4.4, Other Environmental Media).

Genotoxicity. Trichlorobenzenes were not mutagenic in *in vitro* tests with prokaryotic organisms with or without metabolic activation (Haworth et al. 1983; Jorgenson et al. 1976; Kubo et al. 2002; Nohmi et al. 1985; Ono et al. 1992; Schoeny et al. 1979). It is unclear what key information additional studies would provide. 1,2,3-Trichlorobenzene and 1,2,4-trichlorobenzene were cytotoxic to mammalian cells in studies conducted in Chinese hamster V79 cells *in vitro*, a system that lacks metabolic activation capacity, indicating that the effect was due to the parent compound (Fratello et al. 1997). Other studies *in vitro* with mammalian cells also showed 1,2,4-trichlorobenzene to be cytotoxic (Garrett and Lewtas 1983; Shimada et al. 1983). Fratello et al. (1997) suggested that the toxicity of these chemicals was related to their ability to penetrate/perturbate the cellular membranes, but further studies examining this issue would be valuable. Limited studies of the genotoxicity of trichlorobenzenes *in vivo*, mostly micronuclei assays, indicate that these compounds are clastogenic (Mohtashamipur et al. 1987; Parrini et al. 1990). Studies that evaluate whether metabolites of trichlorobenzenes, such as methylsulfones, thought to be responsible for the induction of drug-metabolizing enzymes and alterations in heme metabolism (Kato and Kimura 2002; Kato et al. 1993) could provide insight into the mechanism of action of trichlorobenzenes.

Reproductive Toxicity. There is no information regarding reproductive effects in humans exposed to trichlorobenzenes. A multi-generation reproductive study in rats exposed to 1,2,4-trichlorobenzene in the drinking water is available (Robinson et al. 1981). In that study, 1,2,4-trichlorobenzene did not affect fertility. None of the intermediate-duration oral, inhalation, or dermal studies or the chronic-duration oral studies conducted with trichlorobenzenes reported treatment-related histological alterations in the reproductive organs of male and female animals (Black et al. 1988; CMA 1989; Coate et al. 1977; Côté et al. 1988; Hiles 1989; Kociba et al. 1981; Moore 1994a, 1994b; Rao et al. 1982; Sasmore et al. 1983). Additional studies with 1,2,4-trichlorobenzene or multi-generation studies with 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene do not seem warranted at this time.

Developmental Toxicity. No information was located regarding developmental effects in humans exposed to trichlorobenzenes. The three trichlorobenzene isomers have been tested for potential developmental toxicity in rats (Black et al. 1988; Kitchin and Ebron 1983; Robinson et al. 1981); 1,2,4-trichlorobenzene has also been tested in mice (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986). In all these studies, 1,2,4-trichlorobenzene was administered by oral gavage

3. HEALTH EFFECTS

during pregnancy. Kitchin and Ebron (1983) reported retarded development of the fetuses from rats dosed with 360 mg/kg/day 1,2,4-trichlorobenzene; this dose level also induced significant weight loss in the dams, which may have contributed to the slower fetal development. In the studies in pregnant mice dosed with up to 130 mg/kg/day 1,2,4-trichlorobenzene on Gd 8–12, the chemical did not affect pup's viability or growth, or offspring's locomotor activity or fertility to produce a second generation. In the study by Black et al. (1988) with the three trichlorobenzene isomers, the only significant effect reported was the presence of microscopic alterations in the lenses of the eye of fetuses from rats treated with 150 mg/kg/day; no lesions were observed in fetuses from dams dosed with 75 or 300 mg/kg/day 1,2,4-trichlorobenzene. This lesion was not observed in fetuses from dams dosed with 150, 300, or 600 mg/kg/day 1,2,3-trichlorobenzene, but occurred in fetuses from dams administered 150, 300, or 600 mg/kg/day 1,3,5-trichlorobenzene; however, because no quantitative data were presented, it is not known whether the incidences were dose-related. It seems important to try to duplicate these findings and/or test a different animal species, and to also perform quantitative analyses of the results to obtain dose-response relationships. Since the toxicity of trichlorobenzenes does not seem to be route-dependent, developmental studies by the inhalation and dermal routes do not appear necessary.

Immunotoxicity. No information was located regarding immunological effects in humans exposed to trichlorobenzenes. The information available from studies in animals is limited to results of evaluations of the gross and microscopic morphology of lymphoreticular organs and tissues in some inhalation, oral, and dermal studies conducted with trichlorobenzenes (Black et al. 1988; CMA 1989; Coate et al. 1977; Côté et al. 1988; Hiles 1989; Kociba et al. 1981; Moore 1994a, 1994b; Powers et al. 1975; Rao et al. 1982; Sasmore et al. 1983). For the most part, no significant alterations have been reported. Tests for skin sensitization conducted with 1,2,4-trichlorobenzene or 1,3,5-trichlorobenzene in guinea pigs were negative (Brown et al. 1969; E.I. DuPont 1971; Jorgenson et al. 1976). No studies were located that examined immunocompetence in animals exposed to trichlorobenzenes. Since it is not uncommon to find that subtle changes in immunological parameters occur at exposure levels or doses of chemicals lower than (sometimes much lower) those that produce systemic toxicity, it would be useful to conduct screening studies (Tier I) to assess, for example, cell-mediated and humoral-mediated immunity in rodents exposed to trichlorobenzenes.

Neurotoxicity. No studies were located regarding neurological effects in humans exposed to trichlorobenzenes. Tremors and convulsions were reported in rats and mice administered lethal doses of 1,2,4-trichlorobenzene or 1,3,5-trichlorobenzene (Brown et al. 1969; Jorgenson et al. 1976). Several inhalation, oral, and dermal intermediate- and chronic-duration studies in animals examined the gross and

3. HEALTH EFFECTS

microscopic appearance of the brain, spinal cord, and peripheral nerve and reported no significant alterations (Black et al. 1988; CMA 1989; Coate et al. 1977; Côté et al. 1988; Hiles 1989; Kociba et al. 1981; Moore 1994a, 1994b; Rao et al. 1982; Sasmore et al. 1983). One intermediate-duration inhalation study in monkeys exposed to 1,2,4-trichlorobenzene conducted operant behavior tests in the animals throughout the exposure period and reported no exposure-related alterations (Coate et al. 1977). The data available suggest that the nervous system is not a sensitive target for trichlorobenzenes, but there has not been extensive testing of neurological parameters in animals during prolonged exposure to trichlorobenzenes.

Epidemiological and Human Dosimetry Studies. No epidemiological studies were identified for trichlorobenzenes. It is likely that health evaluations of workers exposed to 1,2,4-trichlorobenzene during the production of this chemical have been conducted at some point, but no data were located in the literature available for review. Studies in animals indicate that the main target for trichlorobenzenes is the liver. Therefore, should a population be identified as being exposed to high levels of trichlorobenzenes, liver function should be monitored with the appropriate tests.

Biomarkers of Exposure and Effect.

Exposure. A biomarker of exposure is an exogenous substance, or its metabolite(s) or the product of the interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (e.g., measurement of the parent compound or its metabolite(s), DNA adducts, etc.).

Body burdens of trichlorobenzenes do not necessarily indicate that exposure to trichlorobenzenes occurred or is occurring because they can also be generated in the body from the metabolism of higher chlorinated benzenes such as tetrachlorobenzenes, pentachlorobenzene, hexachlorobenzene, or the pesticide lindane. Studies of the metabolism of trichlorobenzenes in workers exposed solely to trichlorobenzenes are needed to elucidate a metabolite profile which might include a metabolite that is not produced following exposures to other chlorinated benzenes. This would allow the differentiation between exposures to trichlorobenzenes from exposures to other chlorinated benzenes.

Effect. For the purpose of this data need, a biomarker of effect is a measurable biochemical, physiological, or other alteration within an organism that, depending on the magnitude, can be recognized as an established or potential health impairment or disease.

3. HEALTH EFFECTS

There is virtually no information regarding health effects of trichlorobenzenes in humans, so no specific effect of exposure has been identified. Studies in animals have identified the liver as the main target for trichlorobenzenes toxicity. Even if this were the case in humans exposed to trichlorobenzenes, similar liver alterations can be produced by exposure to many other chemicals. Health evaluations of trichlorobenzene workers may provide useful information regarding health effects that may be specific to exposure to these substances.

Absorption, Distribution, Metabolism, and Excretion. There is virtually no information regarding toxicokinetics of trichlorobenzenes in humans. Studies in animals have shown that trichlorobenzenes are readily absorbed through the gastrointestinal tract following oral exposure (Bakke et al. 1992; Chu et al. 1987; Tanaka et al. 1986), but no information is available regarding absorption through the lungs or the skin. Since trichlorobenzenes are present in outdoor air in cities in the United States (EPA 2010a), absorption studies in animals exposed by inhalation would provide useful information.

Radioactivity derived from the labeled trichlorobenzenes was found widely distributed in tissues of rats and rabbits following administration of single doses of ^{14}C -trichlorobenzenes (Chu et al. 1987; Parke and Williams 1960). Elimination half-lives of 1,2,4-trichlorobenzene from the blood, liver, and kidneys from male rats given a single intraperitoneal injection of the chemical were 5.8, 5.2, and 6.2 hours, respectively (Kato et al. 1993). Elimination half-lives for the other isomers are not available. While short-term studies showed that trichlorobenzenes did not accumulate in tissues, information from repeated-dosing studies is lacking. One 13-week dietary study reported that 1,3,5-trichlorobenzene accumulated at higher levels in fat and liver from rats than 1,2,3-trichlorobenzene or 1,2,4-trichlorobenzene; the levels in fat were one order of magnitude higher than those measured in the liver (Côté et al. 1988).

The only relevant information regarding metabolism of trichlorobenzenes in humans is that in microsomal preparations from human livers, CYP2E1 was the major enzyme in the formation of 2,3,4-trichlorophenol and 2,3,5-trichlorophenol, while CYP3A4 was responsible for the formation of 2,3,6-trichlorophenol (Bogaards et al. 1995). The metabolism of trichlorobenzenes in animals exposed orally and parenterally has been fairly well studied, but no information is available following inhalation or dermal exposure. The specific enzymes involved in the initial formation of phenolic intermediates are not known, but probably involve cytochrome P-450 isozymes. The role of metabolism in the toxicity of 1,2,4-trichlorobenzene has been studied (Kato and Kimura 2002; Kato et al. 1993), but no information is available for the other two

3. HEALTH EFFECTS

trichlorobenzene isomers. A study in which 1,2,4-trichlorobenzene was incubated *in vitro* with microsomes isolated from the liver of male rats reported the formation of quinone metabolites, which bound covalently with microsomal protein and with exogenously added DNA (Den Besten et al. 1991). Further studies are needed to examine whether this can also occur *in vivo* and to determine the role that these metabolites may play in the toxicity of trichlorobenzenes.

Data are available on the elimination and excretion of metabolites of the three trichlorobenzene isomers following single or short-term oral exposure to these chemicals (Chu et al. 1987; Jondorf et al. 1955; Lingg et al. 1982; Parke and Williams 1960; Tanaka et al. 1986). Further information regarding route of excretion in relation to increasing dose levels in single dose studies and in relation to duration of exposure would be useful.

Comparative Toxicokinetics. There are no data regarding toxicokinetics of trichlorobenzenes in humans. Studies in animals have reported qualitative differences in metabolite production and disposition between species. For example, glutathione conjugation was the predominant pathway in rats, whereas glucuronidation was predominant in monkeys (Lingg et al. 1982). The same study also showed that rats excreted 1,2,4-trichlorobenzene-derived radioactivity in the urine 2–3 times faster than monkeys. However, since there are no toxicokinetic data in humans, the animal species that is the most appropriate model for humans is unknown. Analyses of the urine of workers exposed to trichlorobenzenes would provide valuable information.

Methods for Reducing Toxic Effects. No specific methods for the mitigation of effects of acute exposure to trichlorobenzenes were located other than measures to support vital functions. No information was located concerning mitigation of effects of lower-level or longer-term exposure to trichlorobenzenes. This, in part, may reflect the fact that no population has been identified as having been subjected or currently undergoing exposure to excessive amounts of trichlorobenzenes. Therefore, it is difficult to design studies or methods for reducing toxic effects if no significant health effects have been reported to date.

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

3. HEALTH EFFECTS

It is not known whether children are more or less susceptible to the effects of exposure to trichlorobenzenes than adults because there are no studies that specifically addressed this question. There is no information on whether the developmental process is altered in humans exposed to trichlorobenzenes. For the most part, studies in rats and mice did not show trichlorobenzenes to be embryotoxic or teratogenic (Black et al. 1988; Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986; Kitchin and Ebron 1983). However, Black et al. (1988) reported lesions in the lenses of the eye of fetuses from rats dosed with 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22. Since no quantitative data were shown, the shape of the dose-response relationship could not be verified. Replication of these results would be useful. The information available does not suggest that trichlorobenzenes have endocrine-disrupting ability, but this issue has not been systematically studied.

There are no data to evaluate whether pharmacokinetics of trichlorobenzenes in children are different from adults. There is no information on whether trichlorobenzenes can cross the placenta, but they have been detected in human breast milk, so they could be transferred to newborns (Mes et al. 1993; Newsome et al. 1995). There are no data to permit an evaluation of whether metabolism of trichlorobenzenes is different in children than in adults.

Research into the development of sensitive and specific biomarkers of exposures and effects for trichlorobenzenes would be valuable for both adults and children. There are no data on the interactions of trichlorobenzenes with other chemicals in children. There are no pediatric-specific methods to reduce peak absorption, body burdens, or to interfere with the mechanisms of action of trichlorobenzenes. Based on the information available, it is reasonable to assume that the supportive methods recommended for maintaining vital functions in adults will also be applicable to children.

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

3.12.3 Ongoing Studies

No ongoing studies pertaining to trichlorobenzenes were identified in Toxline (2013).

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

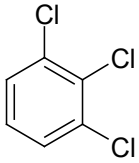
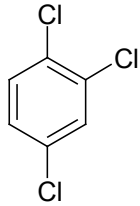
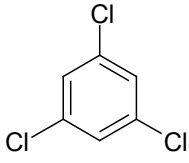
There are three possible isomers for trichlorobenzene: 1,2,3-trichlorobenzene; 1,2,4-trichlorobenzene; and 1,3,5-trichlorobenzene. The chemical identity of each isomer is shown in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Trichlorobenzenes are relatively volatile, hydrophobic substances. The physical and chemical properties of each isomer are shown in Table 4-2.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Trichlorobenzenes^a

Characteristic	1,2,3-Trichlorobenzene	1,2,4-Trichlorobenzene	1,3,5-Trichlorobenzene
Synonym(s)	Benzene, 1,2,3-trichloro-; vic-trichlorobenzene; AI3-15516	Benzene, 1,2,4-trichloro-; unsym-Trichlorobenzene; AI3-07775; 1,2,4-Triclorobenceno (Spanish)	Benzene, 1,3,5-trichloro-; s-Trichlorobenzene; sym-Trichlorobenzene
Chemical formula	C ₆ H ₃ Cl ₃	C ₆ H ₃ Cl ₃	C ₆ H ₃ Cl ₃
Chemical structure			
Identification numbers:			
CAS registry	87-61-6	120-82-1	108-70-3
RTECS	No data	DC2100000 ^b	No data
EPA hazardous waste	No data	No data	No data
EPA/OPP pesticide Code	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	1502	1105	132
EINECS	No data	204-428-0 ^c	No data
NCI	No data	No data	No data

^aAll information from HSDB 2010, unless otherwise noted.^bNIOSH 1994.^cEuropean Communities 2003.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Trichlorobenzenes^a

Property	1,2,3-Trichlorobenzene	1,2,4-Trichlorobenzene	1,3,5-Trichlorobenzene
Molecular weight	181.45	181.45	181.45
Physical description	Platelets from alcohol	Colorless liquid	White crystals
Melting point	51.3°C	16.92°C	62.8°C
Boiling point	218.5°C	213.5°C	208°C
Density	1.4533 g/cm ³ at 25°C	1.459 g/cm ³ at 20°C	1.456 g/cm ³ at 20°C
Odor	No data	Aromatic odor	No data
Solubility:			
Water	18 mg/L at 25°C	49 mg/L at 25°C	6.01 mg/L at 25°C
Organic solvent(s)	Slightly soluble in ethanol; very soluble in ether and benzene. Freely soluble in carbon disulfide	Sparingly soluble in alcohol; miscible with ether, benzene, petroleum ether, carbon disulfide	Sparingly soluble in alcohol; freely soluble in ether, benzene, petroleum ether, carbon disulfide, glacial acetic acid
Partition coefficients:			
Log K _{ow}	4.05	4.02	4.19
Log K _{oc}	3.21–3.90	3.10–4.03	2.80–3.82
Henry's Law constant	1.25x10 ⁻³ atm-m ³ /mol	1.42x10 ⁻³ atm-m ³ /mol	1.89x10 ⁻³ atm-m ³ /mol
Vapor pressure	0.21 mm Hg at 25°C	0.46 mm Hg at 25°C	0.24 mm Hg at 25°C
Autoignition temperature	No data	571°C	No data
Flashpoint	112.7°C	105°C	107°C
Flammability limits in air	No data	Lower flammable limit: 2.5% by volume at 302°F (150°C). Upper flammable limit: 6.6% by volume at 302°F (150°C)	No data
Conversion factors ^b	1 mg/m ³ =0.13 ppm	1 mg/m ³ =0.13 ppm	1 mg/m ³ =0.13 ppm
Explosive limits	No data	2.5–6.6 % volume (at 150°C)	No data

^aAll information from HSDB 2010, unless otherwise noted.

^bVerschueren 2001.

4. CHEMICAL AND PHYSICAL INFORMATION

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

5.1 PRODUCTION

No information is available in the Toxics Release Inventory (TRI) database on facilities that manufacture or process 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 1998c).

Table 5-1 lists the facilities in each state that manufacture or process 1,2,4-trichlorobenzene, the intended use, and the range of maximum amounts of trichlorobenzenes that are stored on site. The data listed in Table 5-1 are derived from the Toxics Release Inventory (TRI12 2013). These data should be used with caution, however, since only certain types of facilities are required to report (EPA 2005b). Therefore, this is not an exhaustive list.

Chlorobenzenes are prepared industrially by reacting liquid benzene with gaseous chlorine in the presence of a Lewis acid catalyst such as ferric chloride (Rossberg et al. 2006). The reaction is carried out at moderate temperature and atmospheric pressure. Generally, mixtures of isomers and compounds with varying degrees of chlorination are obtained, because any given chlorobenzene can react further until hexachlorobenzene is ultimately produced. 1,2,3-Trichlorobenzene and 1,2,4-trichlorobenzene are formed in minor quantities in the production of monochlorobenzene and dichlorobenzene; however, trichlorobenzenes become the primary product if the chlorine input is increased to about 3 moles of chlorine per mole of benzene (Rossberg et al. 2006). 1,2,4-Trichlorobenzene can be obtained more directly via chlorination of 1,4-dichlorobenzene.

An additional method employed to produce 1,2,4- and 1,2,3-trichlorobenzene is based on the dehydrohalogenation of 1,2,3,4,5,6-hexachlorocyclohexane. By reacting hexachlorocyclohexane with aqueous alkali or alkaline earth solutions, ammonia, or other catalysts in the temperature range of 90–250°C, trichlorobenzene is produced. The yield is generally high, ranging between 80 and 99%, with the mixture consisting of 70–85% 1,2,4- trichlorobenzene and 13–30% 1,2,3-trichlorobenzene (Rossberg et al. 2006).

1,3,5-Trichlorobenzene is usually only produced in minor quantities during the chlorination of liquid benzene; however, it can be produced by Sandmeyer reaction on 3,5-dichloroaniline or by reacting

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

Table 5-1. Facilities that Produce, Process, or Use 1,2,4-Trichlorobenzene

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AL	48	0	999,999	2, 3, 4, 6, 7, 10, 11, 12
AR	8	100	99,999	7, 12
AZ	6	1,000	9,999	11, 12
CA	48	100	999,999	4, 7, 8, 9, 10, 11, 12
CT	1	1,000	9,999	1, 3, 7, 11
DE	14	1,000,000	49,999,999	1, 2, 3, 4, 7
FL	10	1,000	99,999	10, 11, 12
GA	23	0	999,999	2, 4, 6, 7, 9, 10, 11
IL	18	1,000	99,999	1, 5, 10, 12
IN	15	100	999,999	2, 3, 7, 9, 11, 12
KS	7	0	499,999,999	9, 12
KY	54	1,000	999,999	1, 3, 5, 6, 9, 10, 12
LA	48	0	999,999	1, 5, 6, 12, 13
MI	12	0	99,999	8, 9, 10, 12
MO	4	0	99,999	9, 12
MS	6	0	999,999	1, 5, 12
NC	145	100	999,999	1, 2, 3, 4, 6, 7, 8, 10, 11, 12
NE	7	1,000	999,999	12
NJ	11	1,000	99,999	7, 9, 11, 12
NY	4	1,000	99,999	9, 10, 12, 13
OH	61	0	49,999,999	7, 8, 9, 10, 11, 12
OK	8	100	9,999,999	1, 10, 12, 13
OR	4	10,000	999,999	12
PA	46	0	9,999,999	1, 2, 3, 5, 7, 9, 10, 12, 13
PR	3	1,000	9,999	7, 10
RI	7	1,000	99,999	2, 9, 10, 12, 13
SC	49	1,000	99,999	2, 3, 6, 7, 8, 9, 10, 12
SD	4	10,000	99,999	12
TN	12	10,000	999,999	10, 12
TX	110	0	49,999,999	1, 2, 3, 5, 6, 7, 9, 10, 11, 12
UT	4	100	99,999	7, 8, 11, 12
VA	27	0	99,999	4, 9, 10, 11, 12
WA	7	1,000	999,999	7, 12

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

Table 5-1. Facilities that Produce, Process, or Use 1,2,4-Trichlorobenzene

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
WI	1	1,000	9,999	10
WV	22	10,000	9,999,999	1, 4

^aPost office state abbreviations used

^bAmounts on site reported by facilities in each state

^cActivities/Uses:

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

Source: TRI12 2013 (Data are from 2012)

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

benzene-1,3,5-trisulfonic acid derivatives with phosgene (Rossberg et al. 2006). It can also be produced by diazotization of 2,4,6-trichloroaniline, followed by treatment with a reducing agent such as hypophosphorous acid (O'Neil et al. 2006).

The EPA Inventory Update Reporting rule requires chemical companies to submit data for compounds manufactured or imported in quantities of $\geq 25,000$ pounds at a single site during a calendar year. For fiscal year 2005, three companies (Ashland Incorporated, BASF Corporation, and PPG Industries, Inc.) reported either manufacturing or importing quantities of 1,2,4-trichlorobenzene in quantities of $>25,000$ pounds (EPA 2010b, 2010e). Two of these corporations (Ashland Incorporated and BASF Corporation) also imported 1,2,3-trichlorobenzene. No data were located for 1,3,5-trichlorobenzene.

5.2 IMPORT/EXPORT

Non-confidential data obtained from the EPA Inventory Update Reporting rule indicated that $<500,000$ pounds of 1,2,3-trichlorobenzene were imported into the United States in 2005 and $1- <10$ million pounds of 1,2,4-trichlorobenzene were imported in 2005 (EPA 2010b, 2010e). No export volumes were located.

5.3 USE

Trichlorobenzenes have primarily been used as solvents and chemical intermediates. In the past, mixed isomers of trichlorobenzene had been used for termite control in soil; however, there are currently no registered uses of trichlorobenzenes as a pesticide (HSDB 2010). 1,2,4-Trichlorobenzene is currently used in solvents in chemical reactions and to dissolve special materials such as oils, waxes, resins, greases, and rubber (Rossberg et al. 2006). It is used as a dye carrier and in the production of dyes (Rossberg et al. 2006). Other uses are associated with textile auxiliaries and as a dielectric liquid (a substance that conducts little or no electricity). 1,2,4-Trichlorobenzene is also one of the most important solvents used for extracting fullerenes from soot (Beer et al. 1997). 1,2,3-Trichlorobenzene is used as an intermediate for the manufacture of pesticides (through the production of 2,3,4-trichloronitrobenzene), and as an intermediate in several fine chemical products and particularly herbicides, pigments, and dyes (Euro Chlor 2002). There is some use of 1,3,5-trichlorobenzene but only as a chemical intermediate and in low quantities (Euro Chlor 2002). In Europe, 1,2,4-trichlorobenzene, has also been used in anti-corrosives paint or rust removing agents and as an additive in polish and maintenance products; however, most of these uses have been discontinued (European Communities 2003). Other former uses of trichlorobenzene include use of the substance in degreasing agents, septic tanks and drain cleaners, wood

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

preservatives, and abrasive formulations (European Communities 2003). Approximately 7,000 metric tons were produced in Europe in 1994–1995 with approximately 75–90% exported (European Communities 2003).

5.4 DISPOSAL

The preferred method of disposal of trichlorobenzene is incineration, preferably after mixing with another combustible fuel (HSDB 2010). Care must be exercised to assure complete combustion to prevent the formation of phosgene. An alkali scrubber is necessary to remove the halo acids produced. Powdered activated carbon treatment (PACT) is used with the activated sludge for waste water treatment of trichlorobenzene (HSDB 2010). Primary treatment consists of neutralization with lime and settling followed by combined powdered activated carbon-activated sludge for secondary/tertiary treatment. Primary sludge consisting of metal salts and unreacted lime is dewatered before disposal in a lined landfill. Powdered activated carbon and return powdered activated carbon treatment sludge are added to the primary effluent as it is fed to aeration tanks. Treated effluent is discharged after first passing through a settling lagoon. Consistency and efficiency of removal varies greatly with reported ranges from 44% for 1,2-dichlorobenzene to 99% for a number of volatile organic compounds. For 1,2,4-trichlorobenzene, 66% was removed.

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

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,2,3-Trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene have been identified in 31, 187, and 4 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for trichlorobenzenes is not known. The frequency of these sites can be seen in Figures 6-1, 6-2, and 6-3.

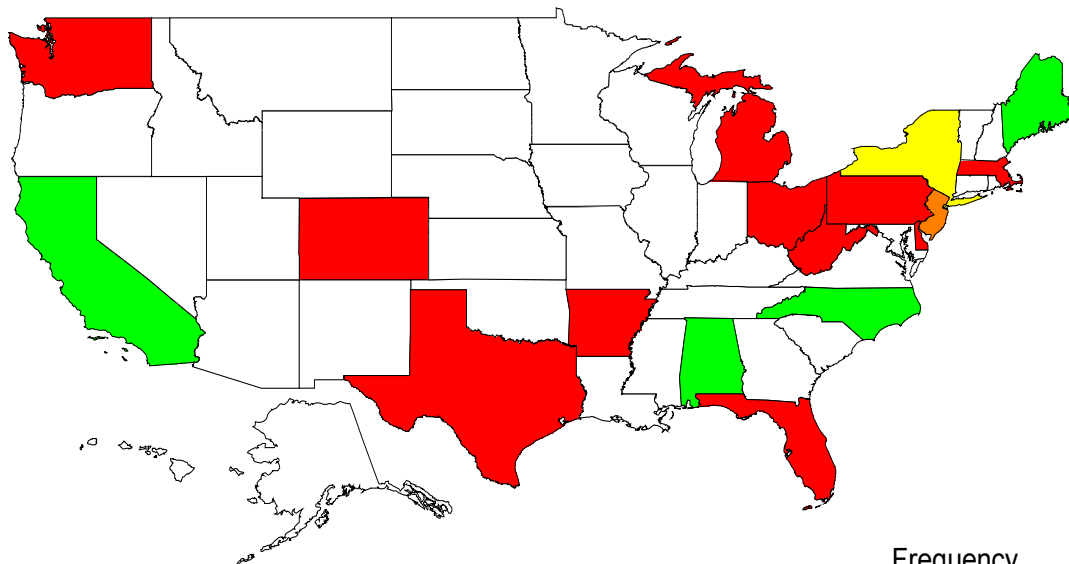
Trichlorobenzenes can be released to the environment from their production and use as solvents, dye carriers and chemical intermediates (Rossberg et al. 2006). They are also formed unintentionally during the combustion of organic materials when chlorine is present and from the degradation of higher chlorinated benzenes, such as tetrachlorobenzene, pentachlorobenzene, and hexachlorobenzene, or the degradation of the pesticide, lindane (γ -hexachlorocyclohexane). Since trichlorobenzenes are minor impurities in mono- and dichlorobenzene; their production and use may also result in the release of trichlorobenzenes to the environment. At one time, mixed isomers of trichlorobenzene were used for the control of termites around the foundations of buildings, which also led to their direct release into the environment. Trichlorobenzenes are volatile substances; consequently, they partition to the atmosphere and are frequently detected in ambient air samples. In addition to being detected in air, trichlorobenzenes have been identified in water, soil, sediment, plants, fish, animals, and food samples. It is often difficult to determine whether levels monitored in environmental samples arise from the direct release of trichlorobenzenes or their unintentional formation from other processes.

1,2,4-Trichlorobenzene is one of 188 chemicals that is designated as a hazardous air pollutant (HAP) under the Clean Air Act. Monitoring data from 2008 indicate that average atmospheric levels in the United States are typically <1 ppbv; however, maximum levels >3 ppbv have been observed (EPA 2010a). In the atmosphere, trichlorobenzenes exist primarily in the vapor phase. Vapor-phase trichlorobenzenes are removed from air by reacting with photochemically produced hydroxyl radicals. The half-life for this reaction is approximately 16–38 days, suggesting that they are susceptible to long-range atmospheric transport.

Trichlorobenzenes volatilize from water surfaces; however, they also tend to adsorb to suspended solids in the water column and partition to sediment, which attenuates the rate at which volatilization occurs.

6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-1. Frequency of NPL Sites with 1,2,3-Trichlorobenzene Contamination



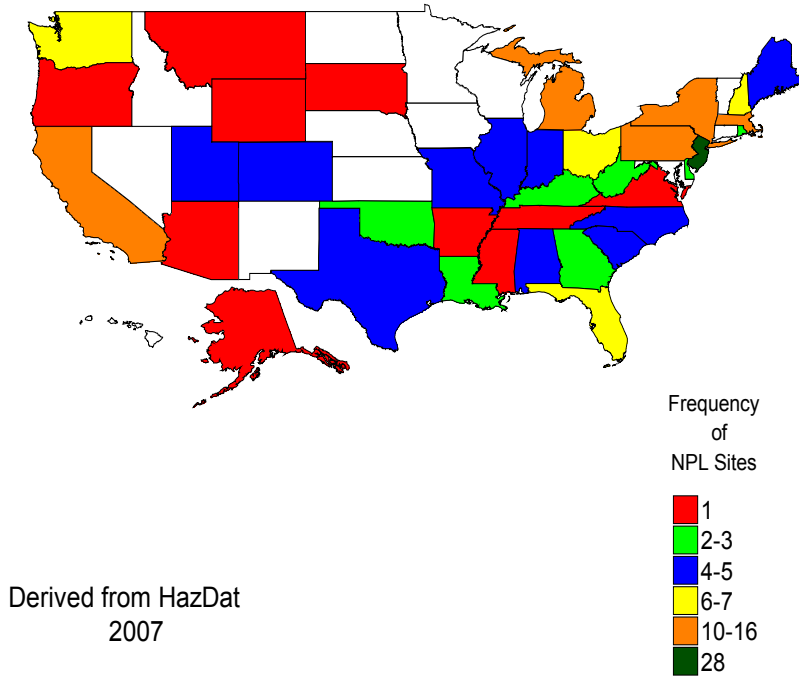
Frequency of NPL Sites



Derived from HazDat
2007

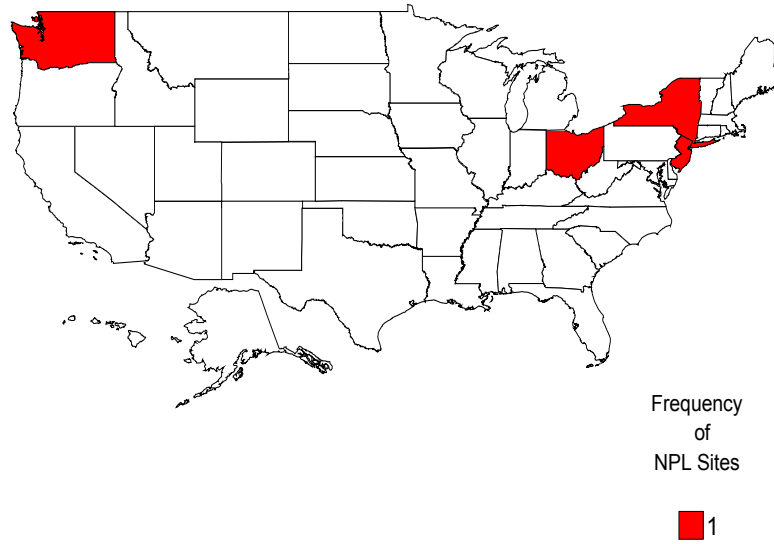
6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-2. Frequency of NPL Sites with 1,2,4-Trichlorobenzene Contamination



6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-3. Frequency of NPL Sites with 1,3,5-Trichlorobenzene Contamination



Derived from HazDat
2007

6. POTENTIAL FOR HUMAN EXPOSURE

The rate of hydrolysis and biodegradation is generally considered slow under environmental conditions. These substances have the potential to bioconcentrate in fish and other aquatic species. Trichlorobenzenes have been detected in surface water, groundwater, and drinking water sources near hazardous waste sites or industrialized areas that produce chlorinated substances. Levels are typically in the parts per trillion (ng/L) range in surface water and drinking water, but vary based on location and emission sources. Trichlorobenzenes have low mobility in soil and typically do not leach into groundwater unless there is a large spill to a soil surface. 1,2,3-Trichlorobenzene and 1,2,4-trichlorobenzene were not detected in an analyses of groundwater samples collected at about 2,400 domestic wells and about 1,100 public wells in a monitoring program conducted by the United States Geological Survey (USGS) to assess groundwater quality in major aquifers in the United States (USGS 2006). However, 1,2,4-trichlorobenzene was detected in groundwater in the ppm range at superfund sites where chlorinated substances were used and disposed of (Carmichael et al. 1999; EPA 1976).

Volatilization is expected to be an important environmental fate process for trichlorobenzenes released to soil; however, adsorption may reduce the rate at which trichlorobenzenes evaporate from soil surfaces. Trichlorobenzenes biodegrade slowly in soils under aerobic conditions, but undergo reductive dechlorination under methanogenic conditions, yielding lower chlorinated species (monochlorobenzene and dichlorobenzenes).

Exposure of the general population to trichlorobenzenes is possible through inhalation of ambient air and ingestion of contaminated food and water. The average daily intake (AVDI) of 1,2,4-trichlorobenzene was estimated to range from 3.34×10^{-5} to 0.0715 mg/kg/day, with ingestion of root crops, fish, and drinking water identified as the primary exposure routes (European Communities 2003). Occupational exposure to trichlorobenzenes is possible through inhalation and dermal contact at workplaces where these substances are manufactured and used.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust

6. POTENTIAL FOR HUMAN EXPOSURE

coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005b).

6.2.1 Air

Estimated releases of 7,110 pounds (~3.2 metric tons) of 1,2,4-trichlorobenzene to the atmosphere from 14 domestic manufacturing and processing facilities in 2012, accounted for about 82% of the estimated total environmental releases from facilities required to report to the TRI (TRI12 2013). These releases are summarized in Table 6-1. There is no information on releases of 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998c).

Section 112 of the Clean Air Act (CAA) lists 1,2,4-trichlorobenzene as one of 188 hazardous air pollutants (HAPs) known to cause or suspected of causing cancer or other serious human health effects or ecosystem damage (EPA 2000b). EPA's National Emission Inventory (NEI) database contains detailed information about sources that emit criteria air pollutants and their precursors, and HAPs for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands (prior to 1999, criteria pollutant emission estimates were maintained in the National Emission Trends [NET] database and HAP emission estimates were maintained in the National Toxics Inventory [NTI] database). The NEI database derives emission data from several sources including state and local environmental agencies, the TRI database, computer models for on-road and off-road emissions, and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of hazardous air pollutants. Table 6-2 provides emissions data for 1,2,4-trichlorobenzene obtained from the NEI in 2005. The total emissions of 1,2,4-trichlorobenzene in 2005 are significantly lower than total emissions from previous years. According to the National-Scale Air Toxic Assessment that used data from the NEI, total emissions of 1,2,4-trichlorobenzene were approximately 264 tons in 2002. Using composite data from the NTI database from 1990 to 1993, it was estimated that the annual emissions of 1,2,4-trichlorobenzene in the United States was nearly 6,000 tons per year during that time frame (EPA 2000b).

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,2,4-Trichlorobenzene^a

State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
AL	2	10	0	0	0	0	10	0	10
GA	1	44	0	0	0	0	44	0	44
KY	1	0	0	0	0	0	0	0	0
LA	2	16	0	0	17	0	16	17	33
MI	1	77	0	0	0	0	77	0	77
OH	2	6,573	0	0	21	250	6,573	271	6,844
PA	2	23	0	0	250	0	23	250	273
TX	3	367	0	1,070	1	0	1,438	0	1,438
Total	14	7,110	0	1,070	289	250	8,181	538	8,719

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

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

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

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

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

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

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

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

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

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

RF = reporting facilities; UI = underground injection

Source: TRI12 2013 (Data are from 2012)

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Emissions of 1,2,4-Trichlorobenzene in 2011

Emission category	Annual emissions (pounds)
Fuel combustion, all processes	4,644.16
Industrial process, transferal categories	208,646.24
Solvent, all categories	199.04
Waste disposal	3,789.73
Total	217,279.20

Source: EPA 2014

6. POTENTIAL FOR HUMAN EXPOSURE

Trichlorobenzenes are also indirectly released to air from combustion processes, such as those that might occur at hazardous waste incinerators. The European Union Risk Assessment for 1,2,4-Trichlorobenzene (European Communities 2003) summarized several combustion experiments, which resulted in the formation of trichlorobenzenes. Plastic waste, including polyethylene and polyvinyl chloride (PVC), was burned in a laboratory scale rotary kiln simulator. Combustion at temperatures exceeding 1,066°C and excess air resulted in the formation of dichlorobenzenes, trichlorobenzenes, pentachlorobenzene, and hexachlorobenzene when polyethylene and PVC were burned together. No chlorinated aromatics were formed, when polyethylene was burned alone. No higher chlorinated (>2) benzenes were formed, when PVC was burned alone (European Communities 2003).

1,2,4-Trichlorobenzene was detected in air samples at nine current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007). The other two isomers, 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene, were not detected in air samples at any of the current or former NPL hazardous waste sites.

6.2.2 Water

There were no estimated releases of 1,2,4-trichlorobenzene to surface water from facilities required to report to the TRI (TRI12 2013). There is no information on releases of 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998c).

1,2,3-Trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene were detected in waste water effluents from treatment plants located along the Niagara River and Grand River in Western, New York at mean concentrations of 2, 11, and 0.3 ng/L, respectively (Oliver and Nicol 1982). 1,2,4-Trichlorobenzene was detected in the industrial effluents of 10 out of 114 industrial sites monitored in the Rhône-Alpes region in France in 1993 (European Communities 2003). Measured levels in these effluents ranged from 9 µg/L (paint manufacturing plant) to 6,150 µg/L (textile dyeing facility).

1,2,3-Trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene were detected in groundwater samples at 20, 114, and 2 current or former NPL hazardous waste sites, respectively, where they were detected in some environmental media (HazDat 2007). 1,2,4-Trichlorobenzene was detected in surface water samples at 18 NPL hazardous waste sites where it was detected in some environmental media

6. POTENTIAL FOR HUMAN EXPOSURE

(HazDat 2007). The other two isomers, 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene, were not detected in surface water samples at any of the NPL hazardous waste sites.

6.2.3 Soil

Estimated releases of 289 pounds of 1,2,4-trichlorobenzene to soils from 14 domestic manufacturing and processing facilities in 2012, accounted for ~3% of the estimated total environmental releases from facilities required to report to the TRI (TRI12 2013). An additional 1,070 pounds (~0.5 metric tons), constituting about 12% of the total environmental emissions, were released via underground injection (TRI12 2013). These releases are summarized in Table 6-1. There is no information on releases of 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998c).

The reductive dechlorination of highly chlorinated benzenes, such as tetrachlorobenzene, pentachlorobenzene, and hexachlorobenzene, results in the formation of trichlorobenzenes in soils and sediment. In addition, the degradation of the pesticide, lindane, has also been demonstrated to result in the formation of 1,2,4-trichlorobenzene (Bharati et al. 1998; Nagpal and Paknikar 2006). Hexachlorobenzene was dechlorinated to tri- and dichlorobenzenes in anaerobic sewage sludge within a three-week incubation period (Fathepure et al. 1988). Greater than 90% of the added hexachlorobenzene was recovered as 1,3,5-trichlorobenzene, and there was no evidence for further dechlorination of 1,3,5-trichlorobenzene. The former use of trichlorobenzenes as a soil treatment to control termite damage around the foundation of buildings also released these compounds directly to the environment; however, the quantitative amount released from this former use is unknown.

1,2,3-Trichlorobenzene, 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene were detected in soil samples at 17, 125, and 1 current or former NPL hazardous waste sites, respectively where they were detected in some environmental media (HazDat 2007). 1,2,3-Trichlorobenzene was detected in sediment samples at 1 NPL site and 1,2,4-trichlorobenzene was detected in sediment samples at 34 NPL sites.

1,3,5-Trichlorobenzene was not detected in sediment samples at any of the current or former NPL hazardous waste sites.

6. POTENTIAL FOR HUMAN EXPOSURE

6.3 ENVIRONMENTAL FATE**6.3.1 Transport and Partitioning**

All three isomers of trichlorobenzene possess vapor pressures and Henry's Law constants (see Table 4-2) that suggest a tendency for these compounds to partition into the atmosphere where they will exist predominantly in the vapor phase. In the atmosphere, trichlorobenzenes have fairly long half-lives and therefore, may be subject to long-range atmospheric transport.

Trichlorobenzenes are expected to possess low mobility in soil given their soil adsorption coefficients. The soil adsorption coefficient (K_{oc}) measured in the upper horizon (0–28 cm depth) of a sandy forest soil obtained from North Carolina (91% sand, 8.4% silt, 0.6% clay) was 2,850 (Njoroge et al. 1998). The K_{oc} value of 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene have been also reported as 1,622 (log K_{oc} 3.21), 10,715 (log K_{oc} 4.03), and 4,898 (log K_{oc} 3.69), respectively (Beck et al. 1995).

Laboratory and field studies demonstrated that volatilization is an important environmental fate process for trichlorobenzenes released to surface water (Wakeham et al. 1983a, 1983b). Volatilization half-lives ranged from approximately 11 days (summer-time conditions) to 22 days (spring-time conditions) for 1,2,4-trichlorobenzene in mesocosm experiments used to simulate ecosystem conditions of Narragansett Bay, Rhode Island (Wakeham et al. 1983a). Trichlorobenzenes are hydrophobic substances that are expected to adsorb to suspended solids and sediment in natural waters. Using water and sediment from the Niagara River, the sediment-water adsorption coefficient of 1,2,4-trichlorobenzene was measured to range from 63,096 to 199,526 (log K_{oc} 4.8–5.3) (Oliver 1987). Other studies have also indicated that trichlorobenzenes adsorb strongly to sediment in the water column. Jonker and Smedes (2000) measured the log K_{oc} values of 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene as 5.79, 6.12, and 5.96, respectively, using water and sediment (0–30 cm depth) from Lake Ketelmeer, the Netherlands. The log K_{oc} values were reported as 5.56 (1,2,3-trichlorobenzene), 5.50 (1,2,4-trichlorobenzene), and 5.36 (1,3,5-trichlorobenzene) using sediment from a deeper (40–120 cm) layer. The rate of adsorption to sediment as well as the extent to which adsorption takes place within the water column may attenuate the rate of volatilization of trichlorobenzenes under environmental conditions.

Trichlorobenzenes have been shown to bioconcentrate in fish. The measured bioconcentration factors (BCF) of 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene measured at different concentrations in carp over a 6-week incubation period are provided in Table 6-3 (NITE 2002). The

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-3. Measured Bioconcentration Factors (BCF) of Trichlorobenzenes in Carp

Isomer	BCF range in carp
1,2,3-Trichlorobenzene	350–980 (concentration 100 µg/L); 130–1,200 (concentration 10 µg/L)
1,2,4-Trichlorobenzene	420–1,140 (concentration 100 µg/L); 120–1,320 (concentration 10 µg/L)
1,3,5-Trichlorobenzene	620–1,620 (concentration 100 µg/L); 150–1,700 (concentration 10 µg/L)

Source: NITE 2002

6. POTENTIAL FOR HUMAN EXPOSURE

mean BCF values of 1,2,4-trichlorobenzene measured in rainbow trout maintained in a flow-through aquarium at initial concentrations of 3.2 and 52 ng/L, were 1,300 and 3,200, respectively, over an exposure period exceeding 100 days (Oliver and Niimi 1983). The mean BCF values of 1,3,5-trichlorobenzene using initial concentrations of 2.3 and 45 ng/L were measured as 1,800 and 4,100, respectively (Oliver and Niimi 1983). American flagfish (*Jordanella floridae*) exposed to 3.8 µg/L (3,800 ng/L) of 1,2,4-trichlorobenzene for 28 days followed by a depuration period of 5–7 days, had a whole-body BCF of 2,026 and the metabolic half-life was estimated to be 1.21 days (European Communities 2003). Spot fish (*Leiostomus xanthurus*) were placed in aquariums containing 10 µg/L (10,000 ng/L) 1,2,4-trichlorobenzene and fed either shrimp exposed to 1,2,4-trichlorobenzene or noncontaminated shrimp over a 28-day exposure period (Heitmuller and Clark 1989). Uptake was determined to occur primarily through the gills rather than accumulation from food. BCF values of 69–135 measured for these fish suggest only modest bioconcentration of 1,2,4-trichlorobenzene and the rapid rate of depuration (half-life of 0.2 days) appeared to be responsible for the lack of accumulation in these fish.

A field study measured the bioaccumulation factor (BAF) of 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene in four aquatic species (mummichog, blue crabs, gulf menhaden and Atlantic croaker) living in an effluent/cooling water canal receiving discharge from a chemical manufacturing plant in the Bayou d'Inde, Louisiana (Burkhard et al. 1997). The lipid-normalized log BAFs for the three species of fish ranged from approximately 4.64 to 4.80 for 1,2,3-trichlorobenzene and 4.68 to 4.86 for 1,2,4-trichlorobenzene (Burkhard et al. 1997). The log BAF for blue crabs were 4.63 and 4.62 for 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene, respectively. These values were found to be consistent with measurements made for trichlorobenzenes in Atlantic croaker, spotted sea trout, blue crabs, and blue catfish obtained from another sampling location of in the Bayou d'Inde (Pereira et al. 1988).

In general, whole-body BCF and BAF values that are >5,000 suggest a high potential for a chemical substance to bioaccumulate under typical environmental conditions, while values <1,000 suggest a much lower potential. Given the range of BCF and BAF values for the trichlorobenzenes, the weight of evidence suggests that these substances may bioconcentrate and bioaccumulate to some extent in the environment, but do not possess the same high degree of bioaccumulation potential as higher chlorinated substances such as hexachlorobenzene.

6. POTENTIAL FOR HUMAN EXPOSURE

6.3.2 Transformation and Degradation**6.3.2.1 Air**

Trichlorobenzenes released to the atmosphere will degrade by reacting with photochemically generated hydroxyl radicals. Degradation by reaction with other common atmospheric oxidants such as nitrate radicals or ozone, and degradation by direct sunlight photolysis are not expected to be important environmental fate pathways. Second-order hydroxyl radical rate constants were estimated using a quantitative structure estimation method (Meylan and Howard 1993). Using these estimated rate constants and assuming a 12-hour hydroxyl radical concentration of 1.5×10^6 hydroxyl radicals per cubic cm of air, estimated half-lives for 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene are 38, 38, and 16 days, respectively.

6.3.2.2 Water

Trichlorobenzenes are expected to biodegrade slowly in water. The rate of aerobic biodegradation of chlorinated aromatic substances decreases as the degree of chlorination on the benzene ring increases. Standardized screening methods used to characterize the capability of rapid mineralization of a substance have determined that trichlorobenzenes and higher chlorinated benzenes are not readily biodegradable under aerobic conditions. A mixture of trichlorobenzene isomers present at 100 mg/L achieved 0% of its theoretical biochemical oxygen demand (BOD) using an activated sludge inoculum at 30 mg/L and the modified MITI test (OECD 301C) over a 28-day incubation period (NITE 2002).

The degradation pattern of 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene was studied using methanogenic water-sediment slurries obtained from nine eutrophic ponds and slow moving streams (Peijnenburg et al. 1992). The degradation pattern was bi-phasic in each water-sediment slurry with an initial half-life range of 62–212 days for 1,2,4-trichlorobenzene and 63–323 days for 1,2,3-trichlorobenzene after a characteristic lag period of approximately 4–8 weeks.

1,2,3-, 1,2,4-, and 1,3,5-Trichlorobenzene were shown to undergo photoreductive dechlorination in water with the presence of a photosensitizing agent, suggesting that photolysis in sunlit surface waters containing natural photosensitizers may be an important environmental fate process (Choudhry et al. 1986). Hydrolysis is not expected to be an important environmental fate process for the trichlorobenzene isomers. The hydrolysis half-life of 1,2,4-trichlorobenzene at pH 7 and 25°C was reported as 3.4 years (USGS 1998).

6. POTENTIAL FOR HUMAN EXPOSURE

6.3.2.3 Sediment and Soil

Degradation of highly chlorinated benzenes is generally slow under aerobic conditions but occurs under methanogenic conditions by reductive dechlorination, yielding lower chlorinated benzenes.

1,2,4-Trichlorobenzene was completely degraded within 4 days using a methanogenic microbial culture isolated from sediment obtained from polluted regions of the Rhine River, Lake Ketelmeer, and an anaerobic waste water treatment plant located in the Netherlands (Middeldorp et al. 1997). 1,4-Dichlorobenzene and monochlorobenzene were observed as the main biodegradation byproducts. The degradation of trichlorobenzenes was studied using sediment obtained from the Rhine River and a municipal water treatment facility in the Netherlands (Bosma et al. 1996). 1,2,4-Trichlorobenzene was partially degraded under aerobic conditions, but only after a long lag time. 1,3,5-Trichlorobenzene and 1,2,3-trichlorobenzene were not degraded under aerobic conditions. Under methanogenic conditions, degradation to mono- and dichlorobenzenes were observed for all three isomers after a 2-month lag period. All three isomers of trichlorobenzene were biodegraded by an acclimated anaerobic sediment slurry using sediment and water from the Tsurumi River, Japan (Masunaga et al. 1996). The first-order biodegradation rate constants for 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene were 0.0299/days, 0.017/days, and 0.0198/days, respectively; corresponding to half-lives were about 23 days (1,2,3-trichlorobenzene), 41 days (1,2,4-trichlorobenzene), and 35 days (1,3,5-trichlorobenzene).

The biodegradation rate of 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene were studied in a Nixon sandy loam under aerobic conditions (Marinucci and Bartha 1979). It was determined that the trichlorobenzenes became increasingly toxic to soil microorganisms at concentrations exceeding 50 µg/g soil and that mineralization proceeded at very slow rates (approximately 0.35 nanomoles/day/20 g soil for 1,2,3-trichlorobenzene and 1.0 nanomoles per day per 20 grams of soil for 1,2,4-trichlorobenzene). Primary degradation products of 1,2,3-trichlorobenzene were identified as 3,4,5-trichlorophenol and 2,4- and 2,6-dichlorophenol. The primary degradation products of 1,2,4-trichlorobenzene were 2,4-, 2,5-, and 3,4-dichlorophenol. 1,2,4-Trichlorobenzene was not significantly biodegraded in soil slurries using a silty loam soil containing 8% organic matter or a loamy sand soil containing 2.6% organic matter over the course of a 30-day incubation period (Brunsbach and Reineke 1994). Trichlorobenzene isomers were extensively degraded under aerobic conditions by enriched microbial cultures that were isolated from contaminated soil samples obtained from a location heavily polluted with electrical transformer fluids (Adebusoye et al. 2007). Both 1,2,3- and 1,3,5-trichlorobenzene were degraded 91% over the course of a 202-hour incubation period using two strains of bacteria isolated from the contaminated soil.

6. POTENTIAL FOR HUMAN EXPOSURE

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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

Concentrations of trichlorobenzenes in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on trichlorobenzenes levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring trichlorobenzenes in a variety of environmental media are detailed in Chapter 7 (Analytical Methods).

6.4.1 Air

The Air Quality System (AQS) database is EPA's repository of criteria air pollutant and hazardous air pollutants monitoring data. Detailed air monitoring data for 1,2,4-trichlorobenzene in various cities in the United States for 2008 are shown in Table 6-4. Data for other years are available as zipped Microsoft Access database files that may be accessed directly from the EPA website. In general, the average concentration of 1,2,4-trichlorobenzene in outdoor air is <1 ppbC (ppbC is equivalent to ppbv multiplied by the number of carbons of the compound) for the majority of the U.S. locations sampled. Maximum concentrations >3 ppbC (0.5 ppbv) were identified at three U.S. cities (Davie, Florida; Hollywood, Florida; Tulsa, Oklahoma). The mean and median daily concentrations of 1,2,4-trichlorobenzene in outdoor air samples in the United States had previously been reported as 0.172 and 0.100 ppbv, respectively (Shah and Singh 1988). Grosjean (1991) reported a maximum concentration of 1,2,4-trichlorobenzene of 0.34 ppbv in measurements of air quality of cities in California. Indoor air concentrations of 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene were reported as <1 $\mu\text{g}/\text{m}^3$ (<0.13 ppbv) at unspecified locations (Brown et al. 1994). Unspecified isomers of trichlorobenzene were reportedly identified in indoor air at two buildings in the United States at a mean concentration of 0.065 ppbv (Otson and Fellin 1992). In a survey of 300 Dutch homes, 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene were measured in indoor air at maximum levels of 28, 33, and 5 $\mu\text{g}/\text{m}^3$ (3.6, 4.3, and 0.65 ppbv), respectively (Otson and Fellin 1992).

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. 1,2,4-Trichlorobenzene Air Levels at Monitoring Stations Throughout the United States in 2008^a

Number of observations	Mean concentration (ppbC) ^a	City	State
23	0.09	Phoenix	Arizona
39	0.103	Phoenix	Arizona
46	0.09	Grand Junction	Colorado
16	0.12	Washington	District of Columbia
32	1.232	Davie	Florida
11	0.09	Davie	Florida
16	1.125	Pompano Beach	Florida
25	1.294	Hollywood	Florida
23	0.817	Not specified	Florida
12	0.09	Not specified	Florida
42	0.205	Tampa	Florida
45	0.206	Plant City	Florida
19	0.497	Tallahassee	Florida
38	0.22	Winter Park	Florida
46	0.203	Saint Petersburg	Florida
45	0.213	Pinellas Park	Florida
14	0.06	Milledgeville	Georgia
11	0.07	Macon	Georgia
13	0.06	Savannah	Georgia
14	0.06	Douglas	Georgia
14	0.06	Not specified	Georgia
29	0.06	Decatur	Georgia
14	0.06	Decatur	Georgia
15	0.06	Rome	Georgia
15	0.06	Not specified	Georgia
15	0.06	Not specified	Georgia
10	0.06	Brunswick	Georgia
19	0.06	Gainesville	Georgia
12	0.06	Warner Robins	Georgia
13	0.06	Valdosta	Georgia
13	0.06	Columbus	Georgia
15	0.06	Not specified	Georgia
12	0.06	Augusta	Georgia
5	0.45	Not specified	Idaho
7	0.45	Boise City (corporate name for)	Idaho
6	0.45	Nampa	Idaho
5	0.45	Not specified	Idaho
42	0.092	Schiller Park	Illinois

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. 1,2,4-Trichlorobenzene Air Levels at Monitoring Stations Throughout the United States in 2008^a

Number of observations	Mean concentration (ppbC) ^a	City	State
49	0.09	Northbrook	Illinois
5	0.09	Northbrook	Illinois
4	0.05	Clarksville	Indiana
51	0.05	Gary	Indiana
13	0.05	East Chicago	Indiana
14	0.05	Whiting	Indiana
16	0.05	Hammond	Indiana
15	0.05	Indianapolis (remainder)	Indiana
16	0.05	Indianapolis	Indiana
15	0.05	Indianapolis (remainder)	Indiana
16	0.05	Ogden Dunes (Wickliffe)	Indiana
14	0.05	Lafayette	Indiana
14	0.05	Evansville	Indiana
25	0.38	Cedar Rapids	Iowa
17	0.329	Des Moines	Iowa
25	0.4	Davenport	Iowa
28	0.12	Essex	Maryland
30	0.12	Beltsville	Maryland
30	0.12	Baltimore	Maryland
31	0.12	Baltimore	Maryland
30	0.506	Sault Ste. Marie	Michigan
5	0.09	Dearborn	Michigan
44	0.01	Rosemount	Minnesota
45	0.01	Inver Grove Heights	Minnesota
48	0.01	Rosemount	Minnesota
48	0.01	Rosemount	Minnesota
50	0.01	Apple Valley	Minnesota
46	0.01	Richfield	Minnesota
49	0.01	Minneapolis	Minnesota
46	0.01	Minneapolis	Minnesota
46	0.01	Minneapolis	Minnesota
50	0.01	Minneapolis	Minnesota
46	0.01	Minneapolis	Minnesota
45	0.01	St. Louis Park	Minnesota
49	0.01	St. Paul	Minnesota
31	0.01	St. Paul	Minnesota
41	0.01	Duluth	Minnesota
46	0.01	St. Paul Park	Minnesota
29	0.01	St. Paul Park	Minnesota

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. 1,2,4-Trichlorobenzene Air Levels at Monitoring Stations Throughout the United States in 2008^a

Number of observations	Mean concentration (ppbC) ^a	City	State
47	0.01	Newport	Minnesota
29	0.01	Bayport	Minnesota
50	0.01	Bayport	Minnesota
10	0.09	Gulfport	Mississippi
12	0.09	Tupelo	Mississippi
46	0.09	St. Louis	Missouri
34	0.09	Camden	New Jersey
43	0.09	North Brunswick Township	New Jersey
44	0.09	Chester	New Jersey
41	0.09	Elizabeth	New Jersey
45	0.05	New York	New York
46	0.11	New York	New York
41	0.08	Lackawanna	New York
39	0.05	Tonawanda	New York
43	0.05	Tonawanda	New York
37	0.05	Tonawanda	New York
46	0.05	Tonawanda	New York
28	0.05	Tonawanda	New York
29	0.05	Not specified	New York
40	0.05	Not specified	New York
45	0.1	New York	New York
45	0.06	Rochester	New York
31	0.07	New York	New York
39	0.07	Niagara Falls	New York
42	0.16	New York	New York
30	0.06	Troy	New York
39	0.09	Troy	New York
39	0.06	Troy	New York
44	0.12	New York	New York
44	0.08	New York	New York
24	0.32	Asheville	North Carolina
26	0.3	Not specified	North Carolina
12	0.37	Charlotte	North Carolina
26	0.33	Candor	North Carolina
24	0.39	Not specified	North Carolina
24	0.36	Not specified	North Carolina
22	0.33	Raleigh	North Carolina
16	0.47	Middletown	Ohio
15	0.38	Cleveland	Ohio

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. 1,2,4-Trichlorobenzene Air Levels at Monitoring Stations Throughout the United States in 2008^a

Number of observations	Mean concentration (ppbC) ^a	City	State
14	0.39	Cleveland	Ohio
15	0.38	Cleveland	Ohio
13	0.39	Cleveland	Ohio
22	0.44	Columbus	Ohio
23	0.46	Steubenville	Ohio
22	0.46	Marietta	Ohio
14	0.09	Not specified	Oklahoma
41	0.09	Tulsa	Oklahoma
5	0.09	Tulsa	Oklahoma
43	0.167	Tulsa	Oklahoma
4	0.09	Tulsa	Oklahoma
44	0.093	Tulsa	Oklahoma
6	0.09	Tulsa	Oklahoma
30	0.06	Not specified	Pennsylvania
24	0.06	Not specified	Pennsylvania
18	0.06	Not specified	Pennsylvania
18	0.06	Chester	Pennsylvania
17	0.06	Marcus Hook	Pennsylvania
22	0.06	Erie	Pennsylvania
31	0.12	Lancaster	Pennsylvania
26	0.06	Lancaster	Pennsylvania
26	0.06	West Norriton	Pennsylvania
32	0.06	Collegeville	Pennsylvania
29	0.07	Philadelphia	Pennsylvania
30	0.09	Philadelphia	Pennsylvania
30	0.1	Philadelphia	Pennsylvania
28	0.07	Philadelphia	Pennsylvania
30	0.05	Philadelphia	Pennsylvania
17	0.06	Not specified	Pennsylvania
31	0.05	Not specified	South Carolina
31	0.05	Not specified	South Carolina
45	0.09	Not specified	South Dakota
46	0.09	Sioux Falls	South Dakota
45	0.09	Loudon	Tennessee
4	0.09	Loudon	Tennessee
45	0.09	Loudon	Tennessee
5	0.09	Loudon	Tennessee
17	0.09	Memphis	Tennessee
47	0.09	Bountiful	Utah

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. 1,2,4-Trichlorobenzene Air Levels at Monitoring Stations Throughout the United States in 2008^a

Number of observations	Mean concentration (ppbC) ^a	City	State
34	0.214	Underhill (town of)	Vermont
18	0.214	Burlington	Vermont
18	0.214	Burlington	Vermont
18	0.214	Rutland	Vermont
18	0.214	Brattleboro (town of)	Vermont
15	0.12	Franconia	Virginia
16	0.12	Not specified	Virginia
16	0.12	Virginia Beach	Virginia
46	0.09	Seattle	Washington
4	0.09	Seattle	Washington

^appbC is equivalent to ppbv multiplied by the number of carbons of the compound.

Source: EPA 2010a

6. POTENTIAL FOR HUMAN EXPOSURE

6.4.2 Water

1,2,4-Trichlorobenzene was detected at mean concentrations of 0.6 and 0.2 ng/L in Lake Ontario and Lake Huron, respectively, in surface water samples collected between April and November of 1980 (Oliver and Nicol 1982). 1,2,3-Trichlorobenzene and 1,3,5-trichlorobenzene were also detected in Lake Ontario at mean concentrations of 0.1 ng/L; however, neither isomer was detected in surface water obtained from Lake Huron. All three isomers of trichlorobenzene were detected in certain locations of the Niagara River. 1,2,3-Trichlorobenzene was identified in three of four sampling locations at concentrations ranging from 2 to 38 ng/L; 1,2,4-trichlorobenzene was identified at four out of four sampling locations at levels ranging from 0.1 to 107 ng/L; and 1,3,5-trichlorobenzene was detected in three out of four sampling locations at levels ranging from 1 to 8 ng/L (Oliver and Nicol 1982). 1,2,3-Trichlorobenzene and 1,2,4-trichlorobenzene were detected at concentrations of 12 and 40 ng/L, respectively, in surface water obtained from the Bayou d'Inde, Louisiana near an industrial plant that produced trichloroethylene and perchloroethylene (Pereira et al. 1988). In surface water obtained from the Niagara River at Niagara on the Lake, 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene were detected at levels of 1.8, 6.4, and 0.7 ng/L, respectively (Fox et al. 1983). During the same sampling period, 1,2,4-trichlorobenzene was detected in Fort Erie water samples at a concentration of 0.1 ng/L. Neither 1,2,3- nor 1,3,5-trichlorobenzene were detected at this location.

Both 1,2,3- and 1,2,4-trichlorobenzene were monitored for, but not detected in, aquifer samples in a comprehensive survey conducted by the USGS of volatile organic compounds in private and public groundwater wells used for drinking water (USGS 2006). Neither isomer was detected in samples obtained from nearly 2,000 public and private wells across the United States. However, 1,2,3-trichlorobenzene was detected in 2 of 19 groundwater wells two years after a polychlorinated biphenyls/trichlorobenzene spill of transformer fluid near Kingston, Tennessee at concentrations of 0.18 and 0.097 mg/L (EPA 1976). 1,2,4-Trichlorobenzene was detected at levels ranging from 4.43 to 5.02 mg/L in groundwater at the Ciba-Geigy Toms River, New Jersey Superfund site, a location that manufactured dyes, pigments, resins, and epoxy additives from 1952 to 1990 (Carmichael et al. 1999).

1,2,3- and 1,2,4-Trichlorobenzene were detected at mean concentrations of 0.1 and 2 ng/L from municipal drinking water samples obtained from three cities in the Lake Ontario region (Oliver and Nicol 1982). Samples were obtained prior to and immediately after chlorine treatment, and no increase in the levels of trichlorobenzene and other chlorobenzenes were observed following chlorination. 1,3,5-Trichlorobenzene was monitored for, but not detected in drinking water at these locations. 1,2,3-Trichlorobenzene

6. POTENTIAL FOR HUMAN EXPOSURE

was detected at a level of approximately 100 ng/L in chlorinated drinking water samples from 2 out of 10 Canadian water treatment plants (Otson et al. 1986).

6.4.3 Sediment and Soil

Chlorobenzenes, including trichlorobenzenes are widespread in Western, New York, particularly in the Niagara Falls region. 1,2,3-Trichlorobenzene was detected in soil samples at mean concentrations of 0.19, 0.54, 0.42, 0.17, and 0.16 ng/g at five locations in Erie County, New York, including the Love Canal area (Ding et al. 1992). 1,2,4-Trichlorobenzene was detected at mean concentrations of 0.96, 2.53, 1.80, 1.00, and 0.48 ng/g in soils at the same five locations. 1,2,4-Trichlorobenzene levels in soil samples in the Toms River Superfund site in New Jersey ranged from below detection limits to 440 ng/g (Carmichael et al. 1999).

Trichlorobenzenes were detected in surficial sediment samples obtained from four of the Great Lakes during sampling conducted between April and November of 1980 (Oliver and Nicol 1982). The results are summarized in Table 6-5. The substantial concentrations of trichlorobenzenes (and other chlorinated substances) observed in the sediment samples obtained from Lake Ontario in comparison to the levels in the other lakes were attributed to the large amount of waste disposal sites and chemical manufacturing plants along the Niagara River leading into Lake Ontario. Suspended solids obtained from the Niagara River contained 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene at levels of 5.4–38, 33–210, and 1.5–23 ng/g, respectively (Fox et al. 1983). 1,2,3-, 1,2,4-, and 1,3,5-Trichlorobenzene were detected at concentrations of 9.6, 306.0, and 83.0 µg/kg (ng/g), respectively, in bottom sediment obtained from the Bayou d'Inde, Louisiana near an industrial plant that produced trichloroethylene and perchloroethylene (Pereira et al. 1988).

1,2,4-Trichlorobenzene was detected in stream bed sediment samples obtained at 1 out of 517 sites in 20 major river basins in the continental United States sampled from August 1992 to September 1995 (Lopes and Furlong 2001). The maximum concentration was reported as 68 µg/kg (ng/g).

6.4.4 Other Environmental Media

Trichlorobenzenes have been detected in a variety of environmental media including plants, fish, animals, and foods. 1,2,4-Trichlorobenzene was identified, not quantified, in various plant material grown in an Illinois coal refuse reclamation site (Webber et al. 1994) and was also present in plants at an average

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-5. The Range and Mean Concentration of Trichlorobenzene Isomers in Sediment Samples Obtained From the Great Lakes

Isomer	Lake Superior (ng/g)	Lake Heron (ng/g)	Lake Erie (ng/g)	Lake Ontario (ng/g)
1,2,3-Trichlorobenzene	ND–1.0 (range); 0.2 (mean)	0.1–1 (range); 0.3 (mean)	0.1–1 (range); 0.4 (mean)	1–16 (range); 7 (mean)
1,2,4-Trichlorobenzene	0.1–4 (range); 1 (mean)	1–26 (range); 6 (mean)	1–9 (range); 3 (mean)	20–220 (range); 94 (mean)
1,3,5-Trichlorobenzene	ND–0.4; 0.2 (mean)	ND–4 (range); 0.7 (mean)	0.1–5 (range); 1 (mean)	7–250 (range); 60 (mean)

ND = Not detected

Source: Oliver and Nicol 1982

6. POTENTIAL FOR HUMAN EXPOSURE

concentration of 0.002 mg/kg in localities contaminated by agrochemical and communal waste (Veningerova et al. 1997).

Catfish obtained from the Bayou d'Inde, Louisiana near an industrial plant that produced trichloroethylene and perchloroethylene had levels of 1,3,5-trichlorobenzene, 1,2,4-trichlorobenzene, and 1,2,3-trichlorobenzene of 480, 3,900, and 770 ng/g, respectively (Pereira et al. 1988). The levels decreased to 250 ng/g (1,3,5-trichlorobenzene), 1,900 ng/g (1,2,4-trichlorobenzene), and 370 ng/g (1,2,3-trichlorobenzene) in catfish obtained 1 mile downstream from the plant. Atlantic croakers, blue crabs, and spotted sea trout obtained 1 mile downstream from the plant had levels of 1,3,5-trichlorobenzene, 1,2,4-trichlorobenzene, and 1,2,3-trichlorobenzene of 50–420, 140–3,200, and 20–710 ng/g, respectively (Pereira et al. 1988). 1,2,3-Trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene were detected in trout from Lake Superior, Lake Huron, Lake Erie, Lake Ontario, and the Niagara River (Oliver and Nicol 1982). Levels of 1,2,3-trichlorobenzene ranged from 0.1 to 1 ng/g, levels of 1,2,4-trichlorobenzene ranged from 0.5 to 5 ng/g, and levels of 1,3,5-trichlorobenzene ranged from 0.1 to 4 ng/g. In each case, the highest levels were obtained from trout in Lake Ontario or the Niagara River. 1,3,5-Trichlorobenzene and 1,2,4-trichlorobenzene were also detected in trout caught near the Niagara River mouth in Lake Ontario at levels of 1.0 and 3.7 ng/g, respectively (Fox et al. 1983).

Hoekstra et al. (2003) measured the levels of persistent chlorinated substances in muscle and liver tissue of Arctic foxes obtained from Holman, Canada, Arviat, Canada, and Barrow, Alaska. Total chlorobenzene levels (1,2-dichlorobenzene, 1,4-dichlorobenzene, 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, 1,3,5-trichlorobenzene, pentachlorobenzene, and hexachlorobenzene) ranged from 4.4 to 17.6 ng/g in muscle tissue and 4.2 to 12 ng/g in liver tissue.

Trichlorobenzene isomers were detected in nine different vegetables collected from supermarkets in Great Britain (Wang and Jones 1994). The results of this study are summarized in Table 6-6. Peattie et al. (1984) identified isomers of trichlorobenzene in seed oils produced from corn, soybean, rape, sunflower, peanut, sesame, walnut, hazelnut, and poppy. 1,2,3-, 1,2,4-, and 1,3,5-Trichlorobenzene were detected in various foods purchased at grocery stores in Ontario, Canada (Davies 1988). Leafy vegetables, fruits, milk, and eggs/meat contained trichlorobenzene levels of 0.11–0.40, 0.12–0.14, 0.14–1.2, and 0.70–0.74 µg/kg, respectively. These results suggest that ingestion of some foods may be a significant source of trichlorobenzene exposure to the general population.

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-6. Trichlorobenzene Concentrations in Whole Vegetables

Vegetable	1,2,3-Trichlorobenzene (µg/kg)	1,2,4-Trichlorobenzene (µg/kg)	1,3,5-Trichlorobenzene (µg/kg)
Carrots	ND	ND	ND
Potato	0.0484	0.0038	0.010
Cabbage	ND	0.0068	0.0225
Cauliflower	ND	0.0309	ND
Lettuce	ND	0.0027	0.0030
Onion	0.0490	ND	0.0363
Beans	ND	ND	ND
Peas	ND	0.0342	0.117
Tomatoes	0.0440	ND	ND

ND = not detected

Source: Wang and Jones 1994

6. POTENTIAL FOR HUMAN EXPOSURE

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to trichlorobenzene from inhalation of ambient air and ingestion of food and drinking water (see Sections 6.4.1–6.4.4 for background environmental levels). In a European Union Risk Assessment Report, four different exposure scenarios were developed to estimate the average daily intake of 1,2,4-trichlorobenzene. The total daily intake was 0.0715 mg/kg/day for the exposure scenario, which yielded the highest estimated total daily intake for humans (European Communities 2003). The estimates suggest that the most important human intake routes are ingestion of root crops, fish, and drinking water. Davies (1988) used the concentration of trichlorobenzene residues in food items purchased in Ontario, Canada and estimated an annual dietary intake of approximately 147 µg/year (0.402 µg/day) for all three combined isomers. MacLeod and Mackay (1999) estimated the daily intake of 1,2,4-trichlorobenzene for residents in Southern Ontario, Canada as 0.3 µg/day, with the greatest contribution arising from inhalation of ambient air (75.4% of the total exposure) followed by ingestion of meat (14.3%), milk (6.4%), and eggs (2.5%).

Trichlorobenzenes have been detected in human body burden studies. Trichlorobenzenes are lipophilic substances, so they tend to concentrate in fatty tissues. In autopsies of Canadian citizens, 1,2,3- and 1,3,5-trichlorobenzene were detected in biopsy fatty tissue at median levels of 1.9 and 1.1 ng/g, respectively, and at maximum levels of 9.1 and 3.7 ng/g, respectively (Mes 1992). Levels were below the detection limits (1.17 ng/g for 1,2,3-trichlorobenzene and 4.02 ng/g for 1,3,5-trichlorobenzene) in blood samples. 1,2,4-Trichlorobenzene was detected in human follicular fluid at a mean concentration of 214 pg/mL for patients undergoing *in vitro* fertilization in Canada (Younglai et al. 2002).

1,2,4-Trichlorobenzene was detected in follicular fluid in over 50% of the patients tested. It was also identified, but not quantified in human female serum obtained at the time of oocyte retrieval for *in vitro* fertilization (Younglai et al. 2002). Serum samples obtained from former residents of Love Canal, New York were examined for the presence of organochlorines, including trichlorobenzene (Kielb et al. 2010). The serum samples had been collected in 1978–1979 and stored by the New York State Department of Health and analyzed between 1999 and 2004. 1,2,4-Trichlorobenzene was detected in 97% of all of the samples studied (detection limit 0.02 ng/g lipid). Median serum levels for 1,2,4-trichlorobenzene of 126.9 ng/g (n=9) were reported for residents living closest to the site when it was still open and 42.2 ng/g (n=67) for residents living on the peripheries of the site. The median levels of 1,2,4-trichlorobenzene in serum samples was 204.2 ng/g (n=171) and 35.9 ng/g (n=213) for residents residing nearer and at the peripheries of the site, respectively, after it was closed and the most toxic portion reburied with dirt and clay (Kielb et al. 2010).

6. POTENTIAL FOR HUMAN EXPOSURE

Occupational exposure to trichlorobenzenes arises from inhalation and dermal contact with these compounds at workplaces where they are produced and used. According to the National Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983, an estimated 691 workers (all employed in the textile mill trade) were potentially exposed to 1,2,3-trichlorobenzene in the workplace (NIOSH 1990a, 1990b). In addition, 4,033 workers, including 1,463 female employees, were potentially exposed to 1,2,4-trichlorobenzene (NIOSH 1990a, 1990b). The NOES database does not contain information on the frequency, concentration, or duration of occupational exposure to any of the chemicals listed. The survey provides only estimates of the numbers of workers for whom potential exposure in the workplace is an issue. Data from the EPA Inventory Update Reporting database indicate that >1,000 workers can be reasonably expected to have some form of exposure to 1,2,4-trichlorobenzene and between 100 and 999 workers are expected to be exposed to 1,2,3-trichlorobenzene in the United States (EPA 2010b, 2010e). However, this database does not indicate the level of exposure or the primary exposure route for these workers. Levels of 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene in the breathing zone at different locations of a chemical warehouse located in Michigan ranged from 0.03 to 0.06 ppmv and 0.57 to 1.4 ppmv, respectively (Dow Chemical 1981). The highest levels were observed in locations where trichlorobenzenes and trichloroethane were being packaged into drums. The NIOSH ceiling limit (concentration not to be exceeded at any time during the work day) is 5 ppmv (37 mg/m³) for 1,2,4-trichlorobenzene (NIOSH 2005).

6.6 EXPOSURES OF CHILDREN

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

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

6. POTENTIAL FOR HUMAN EXPOSURE

Children are exposed to trichlorobenzenes by the same means that adults are: inhalation of ambient air, and ingestion of contaminated food and drinking water. Trichlorobenzenes have also been identified in breast milk; therefore, infants may also be potentially exposed through breast feeding. The mean, median, and maximum concentrations of 1,2,3-trichlorobenzene from 412 breast milk samples obtained from different provinces in Canada in 1986 were 0.98, 0.49, and 18.33 ng/g, respectively, for whole milk samples and 38.7, 15.3, and 466.3 ng/g, respectively, in milk fat (Mes et al. 1993). Only maximum levels of 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene were reported. The maximum levels of 1,2,4-trichlorobenzene in whole milk and milk fat were 17.40 and 4490.9 ng/g, respectively. The maximum levels of 1,3,5-trichlorobenzene in whole milk and milk fat were 5.18 and 128.2 ng/g, respectively. The mean concentrations of 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene in whole milk obtained from 497 breast milk samples in Canada collected in 1992 were reported as 0.07, 0.11, and 0.04 ng/g, respectively (Newsome et al. 1995). The mean concentrations in milk fat were 2.79 ng/g for 1,2,3-trichlorobenzene, 3.81 ng/g for 1,2,4-trichlorobenzene, and 1.40 ng/g for 1,3,5-trichlorobenzene.

No studies were located that expressed the level of trichlorobenzenes or its metabolites in amniotic fluid, meconium, cord blood, or neonatal blood. Children are unlikely to be exposed to trichlorobenzenes from their parents clothing or playing on the ground (soil, carpeting, etc.) due to the volatility of these substances.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

High levels of trichlorobenzenes have been identified in soil and water samples in heavily industrialized areas or at superfund sites such as the Love Canal site in Niagara Falls, New York. Populations residing near these locations may be exposed to higher levels of trichlorobenzenes than the general population. In addition, certain food items have been shown to contain high levels of trichlorobenzenes, in particular fish and root crops. Individuals who consume large amounts of these products may have higher exposures to trichlorobenzenes as compared to the general population.

6.8 ADEQUACY OF THE DATABASE

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

6. POTENTIAL FOR HUMAN EXPOSURE

research designed to determine the health effects (and techniques for developing methods to determine such health effects) of trichlorobenzenes.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties necessary for characterizing the environmental fate of all three isomers of trichlorobenzene have been measured or can be adequately estimated. No data needs have been identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2012, became available in February of 2013. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Data are available through the U.S. EPA Inventory Update Reporting system regarding the levels of trichlorobenzenes that are either manufactured or imported in quantities of $\geq 25,000$ pounds at a single site during a calendar year. Data are available for 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene. No data are available for 1,3,5-trichlorobenzene. Trichlorobenzenes appear to have no significant uses in household products in which the general population may be exposed, but have been identified in food. Sufficient use and disposal data exists for the trichlorobenzenes (HSDB 2010; Rossberg et al. 2006); however, a data need exists to determine the quantity of trichlorobenzenes that may have been exported. A data need also exists to estimate the amount of trichlorobenzenes released to the environment from both direct emissions and indirect releases via the degradation of higher chlorinated benzenes and lindane.

Environmental Fate. Trichlorobenzenes are volatile substances that tend to partition to air and sediment when released to the environment and are generally slow to degrade in the environment

6. POTENTIAL FOR HUMAN EXPOSURE

(European Communities 2003; Peijnenburg et al. 1992; USGS 1998). Sufficient data exists to characterize the transport and environmental fate of trichlorobenzenes and consequently no data needs are identified.

Bioavailability from Environmental Media. Studies characterizing the ADME (Absorption, Distribution, Metabolism, and Elimination) of 1,2,3-, 1,2,4-, and 1,3,5-trichlorobenzene following oral exposure in humans are not available. In addition no ADME, data are available for inhalation and dermal exposure in humans and animals. A data need to determine the bioavailability of trichlorobenzenes from environmental media exists.

Food Chain Bioaccumulation. Trichlorobenzenes have the potential to bioconcentrate and bioaccumulate in the environment and have been quantified in fish (Burkhard et al. 1997; Pereira et al. 1988), animals (Hoekstra et al. 2003) and food crops (Wang and Jones 1994). No data needs are identified.

Exposure Levels in Environmental Media. Monitoring data are available for trichlorobenzenes in air (EPA 2010a; Grosjean 1991; Shah and Singh 1988), water (Carmichael et al. 1999; Fox et al. 1983; Oliver and Nicol 1982; Pereira et al. 1988), soil and sediment (Carmichael et al. 1999; Fox et al. 1983; Pereira et al. 1988), plants (Veningerova et al. 1997; Webber et al. 1994) and food (Davies 1988; Wang and Jones 1994). Human intakes have been estimated from environmental media (European Communities 2003; MacLeod and Mackay 1999). Reliable monitoring data for the levels of trichlorobenzenes in contaminated media at hazardous waste sites are needed so that the information obtained on levels of trichlorobenzenes in the environment can be used in combination with the known body burden of trichlorobenzenes to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Limited studies have shown that trichlorobenzenes have been detected in human blood (Mes 1992), adipose tissue (Mes 1992), follicular fluid (Younglai et al. 2002), and breast milk (Mes et al. 1993) in Canada. Additional studies on exposure levels to the U.S. population are needed.

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

Exposures of Children. Children are exposed to trichlorobenzenes by the same routes that affect adults. Trichlorobenzenes have been detected in breast milk samples collected from Canadian females

6. POTENTIAL FOR HUMAN EXPOSURE

(Mes et al. 1993; Newsome et al. 1995). A data need exists to determine current trichlorobenzene residues and their sources in breast milk of members of the U.S. general population and whether children differ in weight-adjusted intakes of trichlorobenzenes as compared to adult populations.

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

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

Few populations are expected to have high exposures to trichlorobenzenes. Persons residing near hazardous waste sites where chlorinated substances are disposed of may be subject to higher levels of trichlorobenzene than the general population. In addition, certain food items have been shown to contain high levels of trichlorobenzenes, in particular fish and root crops. Individuals who consume large amounts of these products may have higher exposures to trichlorobenzenes as compared to the general population.

6.8.2 Ongoing Studies

No ongoing studies pertaining to trichlorobenzenes were identified in Toxline (2013).

7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Trichlorobenzenes are typically analyzed for in blood, adipose tissue, and breath samples using gas chromatographic (GC) analysis. Detection limits are typically in the ng/g range. Representative methods are summarized in Table 7-1. For analytes such as trichlorobenzenes, electron capture detection (ECD) is often employed since it is highly sensitive to halogenated compounds and is less costly than mass spectrometer (MS) detection systems. However, the specific identification of a compound is determined only by its retention time, which can be subject to shifts or to interference from other non-targeted compounds. GC using a quadrupole mass spectrometer operating in either the select ion monitoring (SIM) mode or the SCAN mode allows for positive identification of the compound.

Blood or tissue samples are typically prepared by homogenizing and extracting the sample using a solvent such as benzene or acetone, followed by centrifugation and filtration (Mes 1992). In order to eliminate potential interferences from the sample matrix, cleanup and fractionation of the filtrate is accomplished with a Florisil® column using hexane as the eluting solvent prior to introduction to the GC. Average recoveries of the trichlorobenzenes from fortified adipose tissue or blood have been reported to exceed 75% (Bristol et al. 1982; Mes 1992). Alternatively, a purge-and-trap method can be employed in which blood samples are warmed while passing an inert gas over the heated samples (Pellizari et al. 1985a). Trichlorobenzene vapors are trapped onto an adsorbent polymeric resin (Tenax®) and released by thermal desorption, followed by analysis with GC/MS or GC/ECD.

7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Blood samples were homogenized with benzene, centrifuged, and filtered	GC/ECD and GC/MS	1.17 ng/g (1,2,3-TCB); 4.02 ng/g (1,3,5-TCB)	75–90	Mes 1992
Blood	Trichlorobenzenes are volatilized from blood by warming the sample and collecting in Tenax cartridges	GC/MS	3 ng/L	80	Pellizzari et al. 1985a
Blood	Samples of whole blood were extracted with hexane, centrifuged, and analyzed by GC/ECD and GC/MS	GC/ECD and GC/MS	0.33–0.55 ng/g	77.2–93.4 (1,3,5-TCB); 80.4–88.4 (1,2,3-TCB)	Bristol et al. 1982
Adipose tissue	Blood samples were homogenized with benzene, centrifuged, and filtered with glass wool	GC/ECD and GC/MS	1.68 ng/g (1,2,3-TCB); 0.90 ng/g (1,3,5-TCB)	79–95	Mes 1992
Breath	Collection on Tenax tubes, dried using calcium sulfate and desorb to GC inlet	GC/MS	No data	No data	Pellizzari et al. 1985b

ECD = electron capture detector; GC = gas chromatography; MS = mass spectrometry; TCB = trichlorobenzene

7. ANALYTICAL METHODS

Trichlorobenzenes can be analyzed in human breath by collecting exhaled air samples onto a Tenax® GC cartridge, followed by drying with calcium sulfate and thermal desorption to a GC/MS (Pellizari et al. 1985b). Detection limits and recoveries for trichlorobenzene were not reported; however, the detection limit and quantification limit for m-dichlorobenzene was 0.27 and 1.37 $\mu\text{g}/\text{m}^3$, respectively, suggesting that similar limits will be observed for trichlorobenzenes (Pellizari et al. 1985b).

7.2 ENVIRONMENTAL SAMPLES

Methods are available for determining the level of trichlorobenzenes in a variety of environmental matrices. A summary of representative methods is shown in Table 7-2. Validated methods, approved by EPA and NIOSH, are available for air, water, soil, and sediment. GC using ECD or GC/MS is the most widely used analytical technique for identifying and quantifying trichlorobenzenes in environmental matrices.

NIOSH Method 5517 summarizes a method to analyze ambient air for the presence of trichlorobenzenes. Air samples are collected by a sampling pump at a flow rate between 0.01 and 0.2 L/minute for a total sample size of 3–12 L, and adsorption occurs onto a charcoal tube or Tenax® GC cartridge.

Identification and quantification is accomplished using GC/ECD following ultrasonic desorption from the charcoal or Tenax® cartridge (NIOSH 1994). EPA Method TO-14 is similar to the previously described NIOSH method; however, collection of ambient air samples is performed using specially prepared passivated stainless steel canisters rather than adsorbant tubes. The collection of ambient air samples in these canisters provides a number of advantages as compared to the adsorbant tubes including:

- (1) convenient integration of ambient samples over a specific time period (e.g., 24 hours);
- (2) remote sampling and central analysis;
- (3) ease of storing and shipping samples;
- (4) unattended sample collection;
- (5) analysis of samples from multiple sites with one analytical system;
- (6) collection of sufficient sample volume to allow assessment of measurement precision and/or analysis of samples by several analytical systems; and
- (7) storage stability for many volatile organic compounds (VOCs) over periods of up to 30 days (EPA 1999).

Detection limits for trichlorobenzenes in ambient air are typically in the low ppbv range.

Trichlorobenzenes in water, soil, and sediment are typically analyzed by GC/MS or GC/ECD after extraction from the environmental matrix. EPA Method 8260B is used to quantitatively analyze a variety of VOCs, including trichlorobenzenes, with GC/MS. Analysis can be performed on contaminated groundwater and surface water, aqueous sludges, caustic liquors, acid liquors, waste solvents, oily wastes,

7. ANALYTICAL METHODS

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection at flow rate of 0.01 and 0.2 L/minute onto sorbent tubes and desorb with hexane	GC/ECD	0.002 mg/m ³	No data	NIOSH 1994 (NIOSH method 5517)
Air	Collection in passivated stainless steel canisters	GC/ECD or GC/MS	ppbv level	No data	EPA 1999 (Method TO-14)
Groundwater and surface water, aqueous sludges	Closed-system purge-and-trap process	GC/MS	0.03–0.04 µg/L ^a	>100	EPA 1996b (Method 8260B)
Water and waste samples	Continuous liquid-liquid extraction or separatory funnel extraction using methylene chloride	GC/ECD	39 ng/L (1,2,3-TCB); 130 ng/L (1,2,4-TCB); 12 ng/L (1,3,5-TCB)	No data	EPA 1994 (Method 8121)
Groundwater	Continuous liquid-liquid extraction or separatory funnel extraction using methylene chloride	GC/MS	10 µg/L	>70%	EPA 2007 (Method 8270D)
Soil and sediment	Soxhlet Extraction using methylene chloride/acetone (1:1) as the extraction solvent or ultrasonic extraction with GPC cleanup	GC/ECD	No data	96% (1,2,3-TCB); 59% (1,2,4-TCB); 102% (1,3,5-TCB)	EPA 1994 (Method 8121)
Soil and sediment	Closed-system purge-and-trap process	GC/MS	0.44 µg/kg	11.4–75.4	EPA 1996b (Method 8260B)
Sediment	Soxhlet Extraction using dichloromethane. Cleanup with GPC	GC/MS	50 µg/kg	No data	Lopes and Furlong 2001
Fruit and vegetables	Homogenize in a blender followed by Soxhlet extraction using hexane/acetone (2:1)	GC/ECD	0.007–0.01 µg/kg	76.5–125 (1,2,3-TCB); 76.0–85.5 (1,2,4-TCB); 77.0–80.2 (1,3,5-TCB)	Wang and Jones 1994

^aValue is dependent upon the GC column used and isomer measured.

ECD = electron capture detector; GC = gas chromatography; GPC = gel permeation chromatography; MS = mass spectrometry; TCB = trichlorobenzene

7. ANALYTICAL METHODS

mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments (EPA 1996b). Purge-and-trap methods such as EPA Method 5035 are usually employed in conjunction with Method 8260B for sample preparation. Detection limits in water and waste samples are generally <1 ppb for trichlorobenzenes; however, the actual value depends upon the specific isomer and GC column used for the analysis. Detection limits in soil and sediment are also <1 ppb. Wang and Jones (1994) described an analytical method using GC/ECD to analyze levels of trichlorobenzenes in fruits and vegetables. Soxhlet extraction using a hexane/acetone (2:1) solvent mixture followed by cleanup using a Florisil® column was used for the sample preparation. Recoveries in fortified samples exceeded 75% for each isomer, and detection limits in the sub-ppb range were reported.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of trichlorobenzenes is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of trichlorobenzenes.

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. There are no unique biomarkers of exposure for trichlorobenzenes other than the parent compound. Methods are available that can detect trichlorobenzenes in blood (Bristol et al. 1982; Mes 1992; Pellizzari et al. 1985a), adipose tissue (Mes 1992), and exhaled breath (Pellizzari et al. 1985b). No data needs are identified. Trichlorobenzenes detected in humans may arise from direct exposure to the parent compound, but may also arise from the metabolism of other chlorinated compounds such as tetrachlorobenzenes, pentachlorobenzene, or hexachlorobenzene.

7. ANALYTICAL METHODS

Effect. There are no unique biomarkers of effect for trichlorobenzenes.

Methods for Determining Parent Compounds and Degradation Products in Environmental

Media. Trichlorobenzene levels in air, water, and food are of most concern for human health. Methods are available to determine levels of trichlorobenzene in air (EPA 1999; NIOSH 1994), water (EPA 1996b), soil (EPA 1996b), sediment (EPA 1996b), and foods (Wang and Jones 1994). These methods are sensitive enough to detect trichlorobenzene levels in environmental matrices that may be a concern to human health. No data needs are identified.

7.3.2 Ongoing Studies

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

No ongoing studies pertaining to trichlorobenzenes were identified in Toxline (2013).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

ATSDR has derived an intermediate-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene based on an increased incidence of centrilobular hepatocyte hypertrophy in male rats administered 1,2,4-trichlorobenzene in the diet for 13 weeks (CMA 1989). The MRL was derived using BMD modeling of incidence data for hepatocyte hypertrophy in male rats. The predicted dose associated with a 10% extra risk (BMD_{10}) for hepatocyte hypertrophy was 33.09 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 14.35 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene based on an increased incidence of hepatocellular hypertrophy in male rats administered 1,2,4-trichlorobenzene in the diet for 104 weeks (Moore 1994a). The MRL was derived using BMD modeling of incidence data for hepatocellular hypertrophy in male rats. The predicted dose associated with a 10% extra risk (BMD_{10}) for hepatocellular hypertrophy was 23.25 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 13.33 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

EPA (IRIS 2010) has established an oral reference dose (RfD) for 1,2,4-trichlorobenzene of 0.01 mg/kg/day based on a NOAEL of 14.8 mg/kg/day for increased adrenal weights in rats exposed to 1,2,4-trichlorobenzene in drinking water (Robinson et al. 1981). The uncertainty factor used in this assessment was 1,000 (10 for extrapolation from laboratory studies, 10 for the protection of sensitive human subpopulations, and 10 to account for a lack of chronic studies). EPA's assessment was conducted in 1991.

EPA has not derived an inhalation reference concentration (RfC) for trichlorobenzenes.

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

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification	No	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No ^a	WHO 2006
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	No	ACGIH 2009
	STEL (15-minute TWA) 1,2,4-Trichlorobenzene TLV-basis (critical effect)	5 ppm ^b Eye and upper respiratory tract irritation	
AIHA	ERPGs	No	AIHA 2010
EPA	AEGLs	No	EPA 2010c
	Hazardous air pollutant 1,2,4-Trichlorobenzene		EPA 2006b 42 USC 7412
	Regulated toxic substances and threshold quantities for accidental release prevention Second AEGL chemical priority list 1,2,4-Trichlorobenzene	Yes No Yes ^c	EPA 2009j 40 CFR 68.130 EPA 2010d
NIOSH	REL (10-hour TWA) 1,2,4-Trichlorobenzene		NIOSH 2005
	Target organs	5 ppm (40 mg/m ³) ^b Eyes, skin, respiratory system, liver, reproductive system	
OSHA	Category of pesticide	Group III ^d	NIOSH 1992
	PEL (8-hour TWA) for general industry	No	OSHA 2009 29 CFR 1910.1000, Table Z-1

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
NATIONAL (cont.)			
DOE	TEELs		
	TEEL-0 ^e		
	1,2,3-Trichlorobenzene	5 mg/m ³	DOE 2010a
	1,2,4-Trichlorobenzene	0.25 ppm (1.5 mg/m ³)	DOE 2010b
	PAC-1 ^f		
	1,2,3-Trichlorobenzene	15 mg/m ³	
	1,2,4-Trichlorobenzene	0.75 ppm (5 mg/m ³)	
	PAC-2 ^g		
	1,2,3-Trichlorobenzene	25 mg/m ³	
	1,2,4-Trichlorobenzene	5 ppm (35 mg/m ³)	
	PAC-3 ^h		
	1,2,3-Trichlorobenzene	500 mg/m ³	
	1,2,4-Trichlorobenzene	40 ppm (300 mg/m ³)	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No	EPA 2009c 40 CFR 116.4
EPA	Drinking water contaminant candidate list	No	EPA 1998a 63 FR 10274
	Drinking water standards and health advisories		EPA 2009d
	1-Day health advisory for a 10-kg child		
	1,2,4-Trichlorobenzene	0.1 mg/L	
	1,3,5-Trichlorobenzene	0.6 mg/L	
	10-Day health advisory for a 10-kg child		
	1,2,4-Trichlorobenzene	0.1 mg/L	
	1,3,5-Trichlorobenzene	0.6 mg/L	
	DWEL		
	1,2,4-Trichlorobenzene	0.35 mg/L	
	1,3,5-Trichlorobenzene	0.2 mg/L	
	Lifetime		
	1,2,4-Trichlorobenzene	0.07 mg/L	
	1,3,5-Trichlorobenzene	0.04 mg/L	
	10 ⁻⁴ Cancer risk	No	
	Master Testing List	Yes ⁱ	EPA 1996a

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	National primary drinking water standards (1,2,4-trichlorobenzene)		EPA 2009e
	MCL	0.07 mg/L	
	Potential health effects from long-term exposure above the MCL	Changes in adrenal glands	
	Common sources of 1,2,4-Trichlorobenzene in drinking water	Discharge from textile finishing factories	
	Public health goal	0.07 mg/L	
	National recommended water quality criteria (1,2,4-trichlorobenzene)	Yes	EPA 2006a
	Human health for the consumption of		
	Water + organism	35 µg/L	
	Organism only	70 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No	EPA 2009i 40 CFR 117.3
	Groundwater monitoring list	Yes	EPA 2009a 40 CFR 264, Appendix IX
c. Food			
FDA	Bottled drinking water		FDA 2010a 21 CFR 165.110
	1,2,4-Trichlorobenzene	0.07 mg/L	
	EAFUS	No	FDA 2010b
d. Other			
ACGIH	Carcinogenicity classification	No	ACGIH 2009
EPA	Carcinogenicity classification		IRIS 2010
	1,2,4-trichlorobenzene	D ^j	
	RfC	No	
	RfD		
	1,2,4-Trichlorobenzene	0.01 mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance (1,2,4-trichlorobenzene)	Yes ^k	EPA 2009g 40 CFR 302.4
	Reportable quantity	100 pounds	
	Effective date of toxic chemical release reporting		EPA 2009i 40 CFR 372.65
	1,2,4-Trichlorobenzene	1/1/1987	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	Extremely hazardous substances and its threshold planning quantity	No	EPA 2009h 40 CFR 355, Appendix A
EPA	TSCA chemical lists and reporting periods	No	EPA 2009b 40 CFR 712.30
	TSCA health and safety data reporting Effective date		EPA 2009m 40 CFR 716.120
	1,2,3-Trichlorobenzene	10/04/1982	
	1,2,4-Trichlorobenzene	10/04/1982	
	1,3,5-Trichlorobenzene	10/04/1982	
	Sunset date		
	1,2,3-Trichlorobenzene	10/04/1992	
	1,2,4-Trichlorobenzene	10/04/1992	
	1,3,5-Trichlorobenzene	10/04/1992	
	RCRA waste minimization PBT priority chemical list (1,2,4-trichlorobenzene)	Yes	EPA 1998b 63 FR 60332
EPA	Standards of performance for equipment leaks of VOC in the synthetic organic chemicals manufacturing industry		EPA 2009f 40 CFR 60 Subpart VV
	Trichlorobenzenes	Yes	
	Organic hazardous air pollutant		EPA 2009k 40 CFR 63, Table 2 to Subpart F
	1,2,4-Trichlorobenzene	Yes	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
NATIONAL (<i>cont.</i>)			
NTP	Carcinogenicity classification	No	NTP 2005

^aGuideline value not established because total trichlorobenzenes occur in drinking water at concentrations below those at which toxic effects may occur, and health-based value would exceed lowest reported odor threshold (WHO 2006).

^bCeiling: the concentration should not be exceeded during any part of the working exposure.

^cTrichlorobenzenes are included on the list of 371 priority chemicals that are acutely toxic and represent the selection of chemicals for AEGL development by the NAC/AEGL committee during the next several years.

^dGroup III pesticides pose minimal risk of adverse acute effects even at relatively high doses.

^eTEEL-0 is the threshold concentration below which most people will experience no adverse health effects.

^fPAC-1 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience discomfort, irritation, or certain asymptomatic, nonsensory effects. However, these effects are not disabling and are transient and reversible upon cessation of exposure.

^gPAC-2 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape.

^hPAC-3 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

ⁱ1,2,4-Trichlorobenzene was originally recommended to the MTL by the TSCA Interagency Testing Committee in 1990 and was removed in 1994 because the TSCA Section 4 Final Rule-Making testing program was completed.

1,2,4-Trichlorobenzene was again recommended to the MTL in 1995 by the Organization for Economic Cooperation and Development (OECD) and by the U.S. EPA Office of Air and Radiation (OAR). The OECD chemical testing program is currently underway by a voluntary testing agreement and the testing needs include SIDS screening data for health effects, environmental effects, and environmental fate and exposure. The OAR chemical testing action development is currently underway and the testing needs for health effects include acute toxicity, neurotoxicity, developmental toxicity and immunotoxicity.

^jD: not classifiable as to human carcinogenicity based on a dermal exposure study in mice that was found inadequate for drawing conclusions as to carcinogenicity in humans.

^kDesignated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act and Section 112 of the Clean Air Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MTL = Master Testing List; NAC = National Advisory Committee; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; SIDS = Screening Information Data Sets; STEL = short-term exposure limit; TEEL = temporary emergency exposure limits; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; VOC = volatile organic compound; VTA = Voluntary Testing Agreement; WHO = World Health Organization

8. REGULATIONS, ADVISORIES, AND GUIDELINES

EPA has designated 1,2,4-trichlorobenzene as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) (EPA 2006b). 1,2,4-Trichlorobenzene is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 100 pounds (EPA 2009g). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10. GLOSSARY

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

Immunological Effects—Functional changes in the immune response.

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

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

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

In Vivo—Occurring within the living organism.

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

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

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

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

Lethal Time₍₅₀₎ (LT₅₀)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

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

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

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

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

10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

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

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

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

10. GLOSSARY

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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

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

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

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

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

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

10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

Toxic Dose₍₅₀₎ (TD₅₀)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

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

10. GLOSSARY

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

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

10. GLOSSARY

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

APPENDIX A

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2,4-Trichlorobenzene
CAS Number: 120-82-1
Date: May 2014
Profile Status: Final Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 21
Species: Rat

Minimal Risk Level: 0.1 mg/kg/day ppm

Reference: CMA. 1989. A three month dietary range-finding study of 1,2,4-trichlorobenzene in rats final report with letter dated 2/2/89 from Chemical Manufacturers Association. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. EPA Document No. 40-98201006. OTS0523023.

Experimental design: Groups of Fisher-344 rats (10/sex/group) were fed a diet containing 0, 200, 600, or 1,800 ppm 1,2,4-trichlorobenzene for 14 weeks; this diet provided doses of 0, 14.6, 45.6, or 133.7 mg/kg/day for males and 0, 17, 52.5, or 150.6 mg/kg/day for females. These doses were calculated by dividing the sum of the weekly doses provided by the investigators by 14 weeks. End points monitored included clinical signs (daily), physical examination (weekly), ophthalmology (initiation and termination), body weight and food consumption (weekly), hematology and clinical chemistry (termination), gross necropsy (all rats at termination), selected organ weights, and histopathology of all major organs and tissues of the control and high-dose group and liver and kidney of the low- and mid-dose groups.

Effect noted in study and corresponding doses: Treatment with 1,2,4-trichlorobenzene did not affect survival rate. Clinical signs were limited to chromodacryorrhea and lacrimation, which occurred more frequently in treated groups, but without dose-response. The test for ocular abnormalities did not reveal compound-related effects. Administration of 1,2,4-trichlorobenzene did not significantly affect body weight or weight gain. Food consumption was significantly higher in the mid- and high-dose groups than in controls. Hematological alterations consisted of decreased mean erythrocyte count (5%), hemoglobin (7%), and hematocrit (5%) in males dosed with 133.7 mg/kg/day and decreased hemoglobin (4%) and hematocrit (4%) in females dosed with 150.6 mg/kg/day. These changes are within the normal range and are not considered biologically significant. Platelets were significantly increased (16%) in males dosed with 133.7 mg/kg/day; the toxicological significance of this finding is unclear. Significant clinical chemistry changes included elevated BUN in high-dose males (12%) and females (20%), elevated total protein, albumin, and calcium in high-dose males, and lower serum AST activity in males dosed with 45.6 mg/kg/day (22%) and 133.7 mg/kg/day (28%). The elevated BUN was consistent with microscopic alterations in kidneys from male rats. The clinical significance of the alterations in protein and calcium were unclear and the lower transaminase activity was not considered of biological significance. Significant changes in organ weight included dose-related increases in absolute and relative liver weight in all male groups and in mid- and high-dose females, and increased absolute and relative kidneys weight and absolute testes weight in males dosed with 133.7 mg/kg/day. No compound-related gross lesions were observed. Histopathological alterations were limited to the kidneys and liver. Kidney lesions were evident in males dosed with 45.6 and 133.7 mg/kg/day and consisted of dilated tubules, granular casts, hyaline droplets, interstitial nephritis, and papillary mineral deposition. In the liver, centrilobular hepatocyte hypertrophy occurred in males dosed with 45.6 and 133.7 mg/kg/day (0/10, 0/10, 5/10, and 10/10) and in females dosed with 150.6 mg/kg/day (0/10, 0/10, 0/10, and 10/10). Hepatocyte hypertrophy

APPENDIX A

was the probable cause of the increases in liver weight. Liver changes were more prominent in males than in females.

Data for renal effects in male rats were not considered for MRL derivation due to the strong possibility that this may be a unique response of the male rat and not relevant for quantitative risk assessment (EPA 1991). Specific indications that this may be the case include the increased incidences of hyaline droplets, granular casts, and tubule dilation, and the fact that none of these lesions occurred in female rats. In addition, since there is not enough evidence to dissociate the interstitial nephritis from the male-specific nephropathy, interstitial nephritis was also not considered for modeling. In support of this position is the fact that interstitial nephritis did not occur in female rats.

Dose and end point used for MRL derivation: BMDL₁₀ of 14.35 mg/kg/day for centrilobular hepatocyte hypertrophy in male rats.

NOAEL LOAEL BMDL₁₀

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes, done by the investigators.

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

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

Other additional studies or pertinent information that lend support to this MRL: The liver was also a target in an additional 3-month study in rats and in a 13-week study in mice. The study in Sprague-Dawley rats evaluated hematology, clinical chemistry and histopathology of the major organ and tissues, and reported histological alterations in the liver, kidneys, and thyroid in the various dose groups (doses ranged from 0.07 to 82 mg/kg/day in males and from 0.11 to 101 mg/kg/day in females) (Côté et al. 1988). However, the investigators provided only a qualitative description of the results regarding histopathology. In that study, high-dose males showed increases of 13 and 20% in absolute and relative liver weight, respectively, and of 31 and 36% in absolute and relative kidneys weight, respectively. Hematology and clinical chemistry tests were unremarkable. In the 13-week study in mice, groups of B6C3F₁ mice (10/sex/group) were administered a diet that provided doses of 0, 67, 850, or 1,222 mg/kg/day to males and 0, 86, 1,183, or 1,345 mg/kg/day to females (Hiles 1989). End points monitored included clinical signs twice daily and body weight and food consumption weekly. Hematology and clinical chemistry tests were conducted at initiation and during week 14. At termination, gross necropsy was conducted, selected organs were weighed, and selected tissues were examined microscopically. The lungs, liver, and kidneys from all groups were examined; other organs from only the control and high-dose group were examined. Final body weight was significantly reduced in high-dose males (9%) and females (8.3%). Cumulative body weight gain was significantly reduced in low-dose males (27%), high-dose males (40%) and high-dose females (33%); these changes were associated with significant reductions in food consumption throughout the study. Ophthalmologic examinations were conducted at initiation and termination. Significant, treatment-related alterations occurred only in the liver from males dosed with ≥ 850 mg/kg/day and females dosed with $\geq 1,183$ mg/kg/day; the

APPENDIX A

respective NOAELs were 67 and 86 mg/kg/day. The lesions consisted of hepatocellular cytomegaly with karyomegaly and hepatocellular atrophy and degeneration. The incidences in males and females were 0/10, 0/10, 10/10, and 10/10 and 0/9, 0/10, 10/10, and 9/9, respectively (one control female and one high-dose female were accidentally killed during the study).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

BENCHMARK MODELING OF HEPATOCELLULAR HYPERTROPHY IN MALE RATS

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the incidence data for centrilobular hepatocyte hypertrophy in male rats from the CMA (1989) study. Only incidences in males were modeled (0/10, 0/10, 5/10, 10/10); incidences in females (0/10, 0/10, 0/10, 10/10) were judged not amenable for benchmark analysis. A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Adequate model fit is judged by three criteria: goodness-of-fit ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest AIC is chosen. The Gamma model was selected for MRL derivation (Table A-1).

APPENDIX A

Table A-1. Model Predictions for the Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Exposed to 1,2,4-Trichlorobenzene

Model	χ^2 Goodness of fit p-value ^a	AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
Gamma^{b,c}	1.00	15.86	33.09	14.35
Logistic	1.00	17.86	41.94	18.95
Log-Logistic ^d	1.00	17.86	40.29	16.74
Log-Probit ^d	1.00	17.86	35.74	16.04
Multistage (1-degree) ^e	0.26	23.05	6.43	4.04
Multistage (2-degree)	0.85	17.29	18.59	8.90
Multistage (3-degree)	0.97	16.31	24.71	10.07
Probit	1.00	17.86	38.66	17.28
Weibull ^b	1.00	17.86	37.74	13.40
Quantal-Linear	0.26	23.05	6.43	4.04

^aValues <0.10 fail to meet conventional goodness-of-fit criteria.

^bPower restricted to ≥ 1 .

^cBest-fitting model. Among models with adequate fit, the model with the lowest AIC was selected (Gamma).

^dSlope restricted to ≥ 1 .

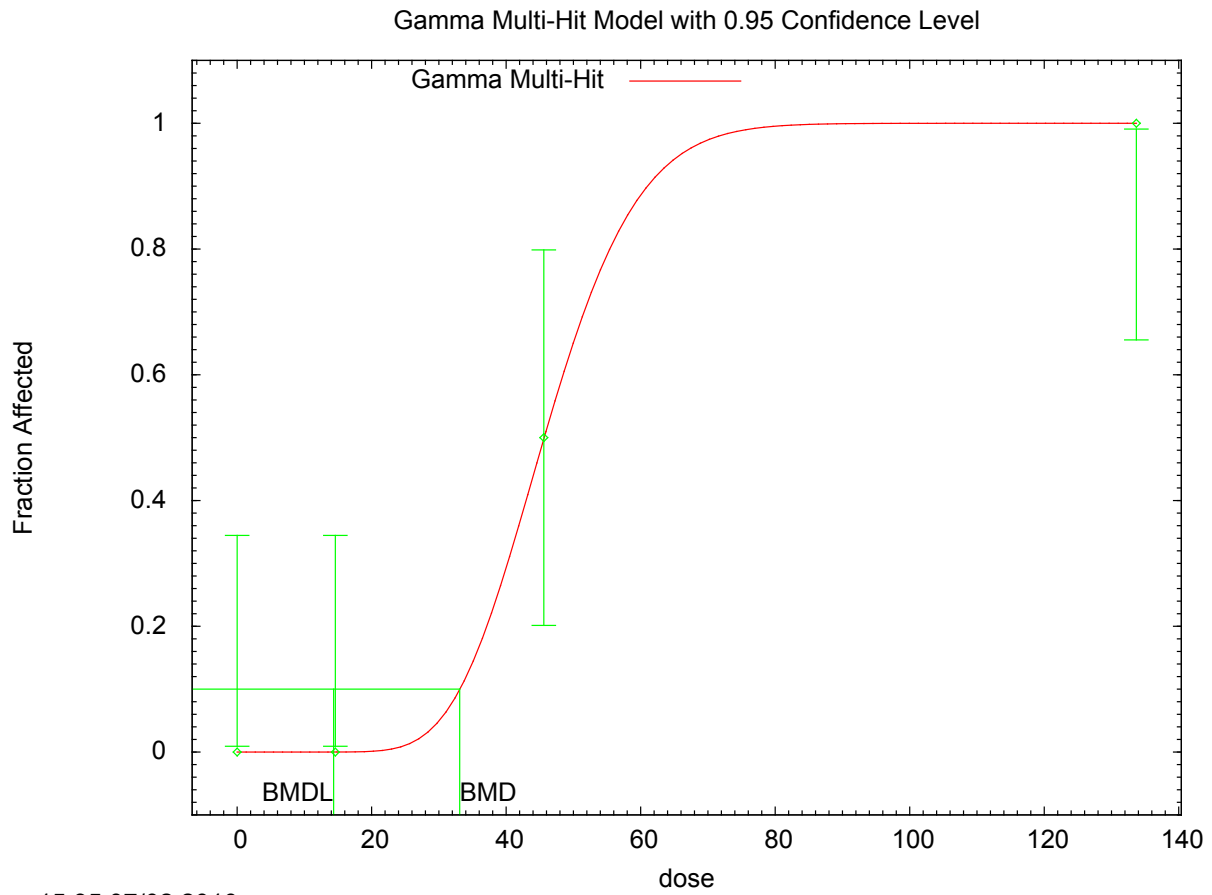
^eBetas restricted to ≥ 0 .

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD

Source: CMA 1989

The dose-response curve is shown in Figure A-1.

Figure A-1. Fit of Gamma Model to Data on 1,2,4-Trichlorobenzene, Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats



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Source: CMA 1989

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2,4-Trichlorobenzene
CAS Number: 120-82-1
Date: May 2014
Profile Status: Final Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 38
Species: Rat

Minimal Risk Level: 0.1 mg/kg/day ppm

Reference: Moore MR. 1994a. Final report (6 copies), 104-week dietary carcinogenicity study with 1,2,4-trichlorobenzene in rats, with cover letter dated 6/15/94. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. EPA Document No. OPPTS-44612. OTS0558832.

Experimental design: Groups of Fisher-344 rats (50/sex/group) were fed a diet containing 0, 100, 350, or 1,200 ppm 1,2,4-trichlorobenzene for 104 weeks. The diet provided doses of 0, 5.6, 19.4, or 66.5 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 6.9, 23.5, or 81.4 mg/kg/day 1,2,4-trichlorobenzene to females. Parameters evaluated included mortality (twice daily), clinical signs, body weight and food consumption (weekly for 16 weeks and every 4 weeks thereafter), hematology (week 52 and 78 for cellular morphology and leukocyte differential, from control and high-dose groups), organ weight (at termination, brain, brainstem, liver, kidneys, testes and epididymis), and gross necropsy and histological examination of all major organs and tissues at termination.

Effect noted in study and corresponding doses: Treatment with 1,2,4-trichlorobenzene resulted in a significant reduction in survival rate in males dosed with 66.5 mg/kg/day. Survival rate in the control, 5.6, 19.4, and 66.5 mg/kg/day males at week 104 were 84, 80, 84, and 60% respectively. There were no distinct or pronounced compound-related differences in clinical signs between treated and control groups. Differences in body weight between treated and control rats were <10% throughout the study. Food consumption was decreased 4–7% in treated groups relative to controls during the study. The only statistically significant hematology findings were a decrease in basophiles at week 52 and monocytes at week 105 in males dosed with 66.5 mg/kg/day, which the investigators considered minor. No evidence of leukemia was noted. Gross necropsy at termination showed increased incidence of liver and kidney abnormalities in males dosed with 19.4 and 66.5 mg/kg/day and a slight increase in incidence of uterine masses in treated females relative to controls; these changes were not discussed any further. Significant changes in organ weight were limited to an increase in absolute and relative liver weight in both male and female rats receiving the highest doses of 1,2,4-trichlorobenzene and a decrease in absolute and relative testes weight in males dosed with 5.6 and 19.4 mg/kg/day. Treatment-related histological alterations were restricted to the liver of males and females and to the kidneys of males and consisted of the following: hepatocellular hypertrophy (which probably caused the increase in liver weight), focal cystic degeneration, diffuse fatty change, transitional renal cell hyperplasia, and increased severity of chronic rat nephropathy in males. Incidences of liver lesions are presented in Table A-2 (note that a smaller number of animals from the low-dose groups were examined for histopathology).

APPENDIX A

Table A-2. Incidence of Liver Lesions in Rats in a 104-Week Dietary Study

Males				
Dose (mg/kg/day)	0	5.6	19.4	66.5
Hepatocellular hypertrophy	2/50(4%)	1/26(3.8%)	5/50(10%)	30/50(60%)
Focal cystic degeneration	9/50(18%)	3/26(11.5%)	4/50(8%)	19/50(38%)
Diffuse fatty change	5/50(10%)	3/26(11.5%)	5/50(10%)	14/50(28%)
Females				
Dose (mg/kg/day)	0	6.9	23.5	81.4
Hepatocellular hypertrophy	6/50(12%)	5/25(20%)	5/50(10%)	37/50(74%)
Diffuse fatty change	15/50(30%)	6/25(24%)	21/50(42%)	30/50(60%)

Source: Moore 1994a

The incidences of transitional cell hyperplasia in the kidneys of male rats were as follows: 0/50, 0/19, 2/50, and 34/50 in males dosed with 0, 5.6, 19.4, and 66.5 mg/kg/day 1,2,4-trichlorobenzene, respectively. Since there is strong evidence from the 14-week study (CMA 1989) suggesting that the renal lesions in male rats may represent a male-specific response not relevant for MRL derivation, and that the renal cell hyperplasia reported in the 104-week study is a typical response seen in the male rat nephropathy, renal cell hyperplasia was not considered as a potential end point for MRL derivation.

Table A-2 shows that: (1) diffuse fatty change was significantly increased in males and females only at the highest dose; (2) focal cystic degeneration occurred at lower incidence in the low- and mid-dose males compared to controls, and was significantly increased only at the highest dose; (3) hepatocellular hypertrophy in female rats occurred at increased frequency only at the highest dose; and (4) only hepatocellular hypertrophy in male rats exhibited dose-response characteristics. Based on these facts, only the hepatocellular hypertrophy in male rats was considered for MRL derivation.

Dose and end point used for MRL derivation: BMDL₁₀ of 13.33 mg/kg/day for hepatocellular hypertrophy in male rats.

NOAEL LOAEL BMDL₁₀

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes, done by the investigators.

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

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

Other additional studies or pertinent information that lend support to this MRL: Treatment of B6C3F₁ mice with 1,2,4-trichlorobenzene in the diet for 104 weeks produced hepatocellular carcinoma (Moore

APPENDIX A

1994b). Two intermediate-duration studies in rats and one in mice also suggested that the liver is a target for 1,2,4-trichlorobenzene (CMA 1989; Côté et al. 1988; Hiles 1989).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

BENCHMARK MODELING OF HEPATOCELLULAR HYPERTROPHY IN MALE RATS

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data set for hepatocellular hypertrophy in the liver of male rats. A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Adequate model fit is judged by three criteria: goodness-of-fit ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest AIC is chosen. Details of the modeling are presented below in Table A-3 and Figure A-2.

Table A-3. Model Predictions for the Incidence of Hepatocellular Hypertrophy in Male Rats

Model	χ^2 Goodness of fit p -value ^a	AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
Gamma ^b	0.92	131.09	23.40	13.76
Logistic	0.95	129.18	25.44	20.54
Log-Logistic ^c	0.91	131.10	23.34	14.03
Log-Probit ^c	0.96	131.08	22.72	14.39
Multistage (1-degree) ^d	0.06	135.48	10.13	7.62
Multistage (2-degree)^{d,e}	0.98	129.12	23.25	13.33
Multistage (3-degree) ^d	0.87	131.11	23.94	13.02
Probit	0.92	129.24	22.92	18.65
Weibull ^b	0.88	131.11	23.95	13.62
Quantal-Linear	0.06	135.48	10.13	7.62

^aValues <0.10 fail to meet conventional goodness-of-fit criteria.

^bPower restricted to ≥ 1 .

^cSlope restricted to ≥ 1 .

^dBetas restricted to ≥ 0 .

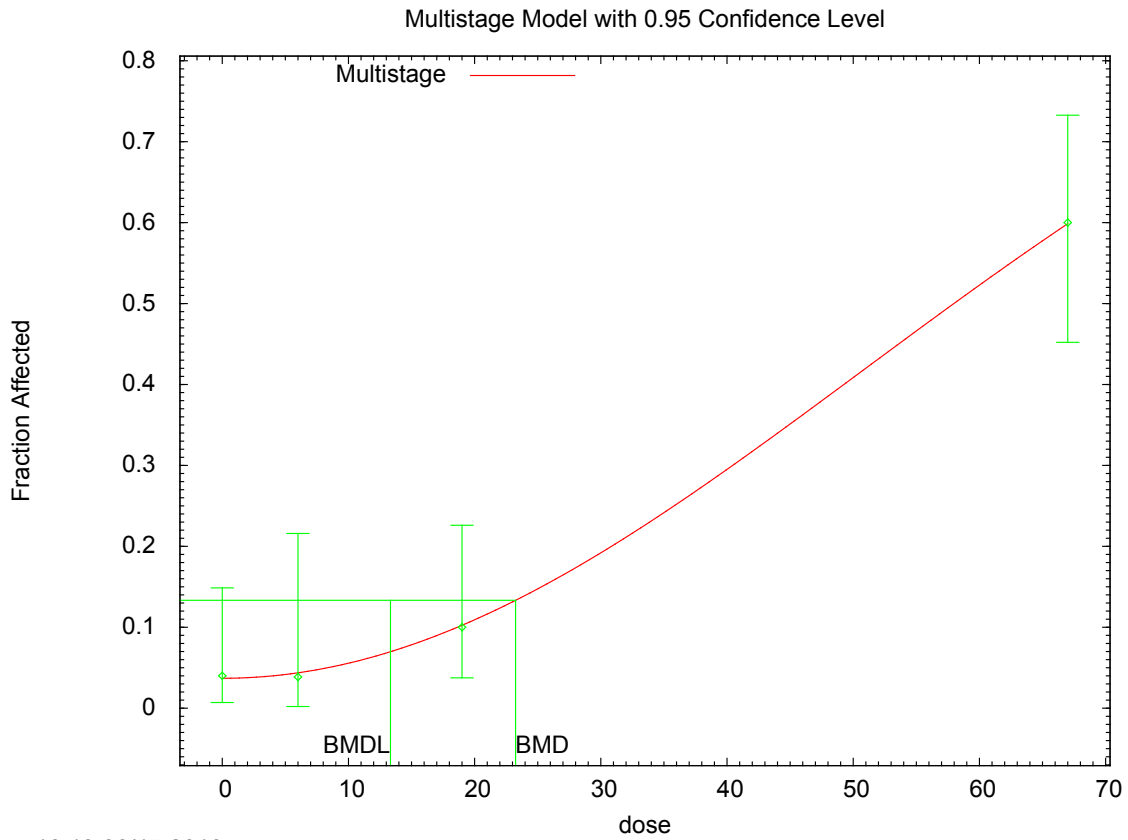
^eBest-fitting model. Among models with adequate fit, the model with the lowest AIC was selected (Multistage 2-degree model).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD

Source: Moore 1994a

In accordance with the selection criteria mentioned above, the Multistage (2-degree) model was selected for MRL derivation. The dose-response curve is shown in Figure A-2.

Figure A-2. Fit of Multistage (2-degree) Model to Data on 1,2,4-Trichlorobenzene, Incidence of Hepatocellular Hypertrophy in Male Rats



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Source: Moore 1994a

APPENDIX A

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

APPENDIX B

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

APPENDIX B

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

- (1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).
- (7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

APPENDIX B

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

- (9) **LOAEL.** A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) **Reference.** The complete reference citation is given in Chapter 9 of the profile.
- (11) **CEL.** A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) **Footnotes.** Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

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

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

- (13) **Exposure Period.** The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.
- (14) **Health Effect.** These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) **Levels of Exposure.** Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) **NOAEL.** In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) **CEL.** Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

APPENDIX B

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

SAMPLE

1 →

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

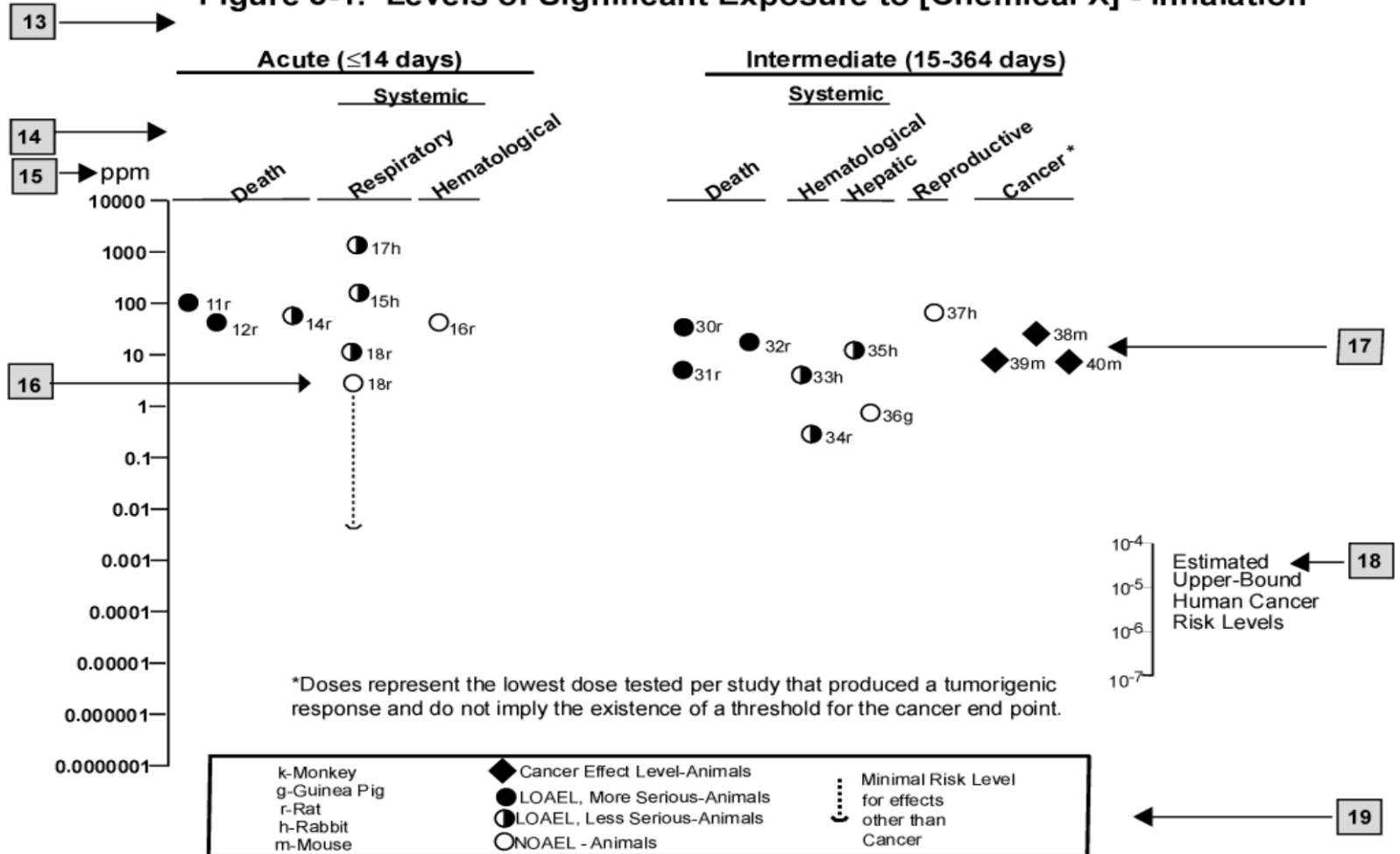
Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC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

12 →

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

SAMPLE

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



APPENDIX B

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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

APPENDIX C

DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F ₁	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K _d	adsorption ratio
kg	kilogram
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid

APPENDIX C

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

APPENDIX C

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

APPENDIX C

>	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

APPENDIX C

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APPENDIX D. INDEX

absorbed dose.....	114, 122, 133
adipose tissue	116, 134, 189, 191, 195
adrenal gland.....	21, 48, 103, 116, 200
adrenals	17, 20, 87, 93, 116
adsorption.....	163, 169, 193
aerobic.....	11, 163, 172, 173
alanine aminotransferase (see ALT)	85
ALT (see alanine aminotransferase)	85
ambient air	12, 115, 159, 163, 185, 187, 193
anaerobic	168, 173
anemia	12, 32
aspartate aminotransferase (see AST).....	22
AST (see aspartate aminotransferase).....	22
bioaccumulation.....	171
bioavailability	189
bioconcentration factor	169
biodegradation.....	163, 172, 173
biomarker	132, 133, 134, 145, 148, 191, 195, 196
blood cell count.....	46
body weight effects	49, 88, 105
breast milk.....	5, 117, 132, 148, 186, 187, 189
cancer	4, 15, 106, 131, 142, 164
carcinogenic	15, 31
carcinogenicity	4, 15, 94, 107, 140, 143, 202
carcinoma.....	15, 26, 94, 107, 142
cardiovascular effects.....	33, 82, 95
cholinesterase.....	134
chromosomal aberrations	112
death.....	31, 32, 51, 52, 94, 106, 202
deoxyribonucleic acid (see DNA).....	107, 110
dermal effects.....	48, 88, 103
developmental effects	51, 92, 93, 106, 143, 147
DNA (see deoxyribonucleic acid).....	107, 109, 110, 121, 128, 133, 145, 147
elimination rate	114
endocrine.....	48, 88, 129, 148
endocrine effects	48, 87, 103
erythema.....	103, 104
estrogenic	130
fetal tissue	92
fetus.....	130, 131
gastrointestinal effects	46, 82, 95
general population.....	12, 115, 142, 143, 163, 183, 185, 187, 188, 190, 202
genotoxic.....	31, 107
genotoxicity.....	107, 112, 143
groundwater	2, 6, 11, 163, 167, 180, 193
half-life.....	2, 11, 133, 159, 171, 172
hematological effects	46, 83, 95

APPENDIX D

hepatic effects	46, 84, 95
hydrolysis	163, 172
hydroxyl radical	11, 159, 172
immunological	31, 49, 90, 144
immunological effects.....	49, 144
K_{ow}	151
LD_{50}	51, 52, 94, 134
leukemia.....	25, 84
lymphoreticular	49, 50, 90, 144
metabolic effects	49, 89
micronuclei	112, 143
milk	5, 12, 91, 135, 183, 185, 187, 190
musculoskeletal effects	46, 84, 95
neonatal	187
neoplastic	26, 86
neurobehavioral.....	129
neurological effects.....	50, 90, 106, 144
ocular effects.....	48, 88, 105
pharmacodynamic	124
pharmacokinetic	124, 125, 126, 130, 132, 148
photolysis	172
placenta	148
rate constant	172, 173
renal effects.....	23, 47, 86, 103
reproductive effects.....	50, 51, 91, 106, 143
respiratory effects.....	33, 52, 95
retention	115, 191
systemic effects.....	32, 33, 52, 95, 134
T3	34, 53, 96
thyroid.....	14, 18, 22, 27, 28, 29, 30, 48, 87, 88, 103, 141, 142
toxicokinetic.....	31, 113, 146, 147
tremors	52
tumors	106, 140, 142
vapor phase	159, 169
vapor pressure	169
volatility	187
volatilization	11, 159, 169

