TOXICOLOGICAL PROFILE FOR DICHLOROBENZENES

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

August 2006

DISCLAIMER

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

UPDATE STATEMENT

A Toxicological Profile for dichlorobenzenes, Draft for Public Comment was released in September 2004. This edition supersedes any previously released draft or final profile.

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

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

Julie Louise Gerberding, M.D., M.P.H.
Administrator
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*Legislative Background

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (770) 488-4178
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

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

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@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, 55 West Seegers Road, Arlington Heights, IL 60005 • 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 Research Implementation 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 1,2-, 1,3-, and 1,4-dichlorobenzenes. The panel consisted of the following members:

1. Dr. Olen Brown, Emeritus Research Professor, University of Missouri, 527 North Cedar Lake Drive West, Columbia, Missouri;

2. Dr. Robert Michaels, President, RAM TRAC Corporation, 3100 Rosendale Road, Schenectady, New York; and

3. Dr. Clint Skinner, President, Skinner Associates, 3985 Shooting Star Road, Creston, California.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about dichlorobenzenes (DCBs) and the effects of exposure to them.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. 1,2-, 1,3-, and 1,4-Dichlorobenzene have been identified in at least 281, 175, and 330, respectively, of the 1,662 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that the number of sites at which dichlorobenzenes are found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

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

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

1.1 WHAT ARE DICHLOROBENZENES?

Each of the three types of DCBs (i.e., 1,2-DCB, 1,3-DCB, and 1,4-DCB) contains two chlorine atoms connected to one benzene molecule. 1,2-DCB is a colorless to pale yellow liquid used to make herbicides. 1,3-DCB is a colorless liquid used to make herbicides, insecticides, medicine, and dyes. 1,4-DCB, the most important of the three chemicals, is a colorless to white solid. It

smells like mothballs and it is one of two chemicals commonly used to make mothballs. 1,4-DCB also is used to make deodorant blocks used in garbage cans and restrooms, and to help control odors in animal-holding facilities. 1,4-DCB has been used as an insecticide on fruit and as an agent to control mold and mildew growth on tobacco seeds, leather, and some fabrics. Recently, using 1,4-DCB to make resins has become very important.

When a package of 1,4-DCB is opened, it 'sublimates', that is, it slowly changes from a solid into a vapor, and enters the atmosphere. The vapor acts as a deodorizer and insect killer. Most of the 1,2-, 1,3-, and 1,4-DCB released into the environment is present as a vapor. DCBs can burn, but they do not burn easily. Most people begin to smell 1,4-DCB when it is in the air at a concentration of 0.18 parts per million (ppm) and 0.011 ppm in water.

DCBs do not occur naturally; chemical companies produce them to make products for home use and other chemicals such as herbicides and plastics. More information about the properties and uses of 1,2-, 1,3-, and 1,4-DCB is provided in Chapters 4 and 5.

1.2 WHAT HAPPENS TO DICHLOROBENZENES WHEN THEY ENTER THE ENVIRONMENT?

Most of the 1,4-DCB enters the environment when it is used in mothballs and in toilet-deodorizer blocks. Some 1,4-DCB is released to the air by factories that make or use it, and only a little is released to soil and water. Very little 1,4-DCB enters the environment from hazardous waste sites. Some 1,2- and 1,3-DCBs are released into the environment when used to make herbicides and when people use products that contain these chemicals. Companies that make 1,4-DCB also make unwanted amounts of 1,2-DCB during the process. 1,2-DCB is released to the environment when companies dispose of these unwanted supplies.

Because DCBs do not dissolve easily in water, the small amounts that enter water quickly evaporate into the air. If they are released to groundwater, they may be transported through the ground to surface water. Sometimes, DCBs bind to soil and sediment. DCBs in soil usually are

not easily broken down by soil organisms. Evidence suggests that plants and fish absorb DCBs. 1,4-DCB has been detected at concentrations of up to 470 parts per billion (ppb) in fish.

More information about DCBs in the environment is provided in Chapters 5 and 6.

1.3 HOW MIGHT I BE EXPOSED TO DICHLOROBENZENES?

Humans are exposed to 1,4-DCB mainly by breathing vapors from 1,4-DCB products used in the home, such as mothballs and toilet-deodorizer blocks. Reported levels of 1,4-DCB in some homes and public restrooms have ranged from 0.291 to 272 parts of 1,4-DCB per billion parts (ppb) of air. 1,2- and 1,3-DCB are not found frequently in the air of homes and buildings because, unlike 1,4-DCB, these chemicals are not used in household products. Outdoor levels of 1,4-DCB range from 0.01 to 1 ppb and are much lower than levels in homes and buildings. Levels in the air around hazardous waste sites are low and range from 0.01 to 4.2 ppb. Outdoor air levels generally range from 0.01 to 0.1 ppb for 1,2-DCB and from 0.001 to 0.1 ppb for 1,3-DCB.

DCBs have been found in samples of drinking water from surface water sources. 1,4-DCB was found in 13% of surface water samples collected during a national survey. These samples contained about 0.008–154 ppb of 1,4-DCB. DCBs also have been found in drinking water from wells but at low concentrations. DCBs are found only infrequently in soil, but they have been detected in soil around hazardous waste sites in the United States.

DCBs have been detected in beef, pork, chicken, eggs, baked goods, soft drinks, butter, peanut butter, fruits, vegetables, and fish. However, the levels of DCBs in foods are generally low.

The average daily adult intake of 1,4-DCB is about 35 micrograms (μg), which comes mainly from breathing 1,4-DCB vapors released from products in homes and businesses. The average daily adult respiratory exposure of the other DCBs is about 1.8 μg for 1,2-DCB and about 0.8 μg for 1,3-DCB.

Individuals can be occupationally exposed to DCBs in workplace air at much higher levels than the general public is exposed. Levels measured in the air of factories that make or process 1,4-DCB products have ranged from 5.6 to 748 ppm of air. In addition, people who live or work near industrial facilities or hazardous waste sites that have high levels of DCBs may have greater exposure to these compounds due to emissions from the facilities and waste sites. People who work or live in buildings where air fresheners, toilet block deodorants, or moth balls containing 1,4-DCB are used also are expected to have a higher exposure to this compound, which could occur from skin contact as well as by breathing.

More information on how you could be exposed to DCBs is given in Chapter 6.

1.4 HOW CAN DICHLOROBENZENES ENTER AND LEAVE MY BODY?

The main way DCBs enter your body is through the lungs when you breathe in DCB vapors released in the workplace or in the home from use of products that contain it. When you breathe in these chemicals for a few hours, it is likely that some of the DCBs that have entered your body will get into your bloodstream.

DCBs also can get into your body if you drink water or eat certain foods that contain them, such as meat, chicken, eggs, or fish. Most of the DCBs that enter your body from food and water will get into your bloodstream. It is not likely that DCBs will enter your body through the skin if you touch products that contain them.

1,4-DCB used in the home could be accidentally swallowed, especially by young children. This possibility exists because household products that contain 1,4-DCB, particularly some kinds of mothballs and deodorant blocks, might be freely available in closets or bathrooms.

Most of the DCB that enters your body (perhaps more than 95%) leaves through the urine in less than a week. Small amounts (perhaps 1–2%) leave your body in the feces and in the air you breathe out. Tiny amounts remain in your fat and might stay there for a long time.

Most of the DCBs that enter your body are changed into other chemicals, mainly dichlorophenols. It is not known if these breakdown products are more or less harmful than the DCBs themselves.

More information about how DCBs enter and leave the body is found in Chapter 3.

1.5 HOW CAN DICHLOROBENZENES AFFECT MY HEALTH?

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

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Most of the information on health effects of DCBs is from studies of 1,2- and 1,4-DCB. Very little is known about the health effects of 1,3-DCB, especially in humans, but they are likely to be similar to those of the other DCBs.

Inhaling the vapor or dusts of 1,2-DCB and 1,4-DCB at very high concentrations could be very irritating to your eyes and nose and cause burning and tearing of the eyes, coughing, difficult breathing, and an upset stomach. These concentrations could occur in workplaces, but are much higher than you would be exposed to in the home. 1,4-DCB is the only DCB that is commonly used in household products (mainly mothballs and toilet-deodorizer blocks). Scientists have no clear evidence that the moderate use of common household products containing 1,4 DCB will cause any problems to your health. A recent study reports limited evidence suggesting that inhalation exposure to 1,4-DCB may result in decreases in lung function. Some people reported

health problems, such as dizziness, headaches, and liver problems, from very high levels of 1,4-DCB in the home. However, these people used very high amounts of 1,4-DCB products and continued to use the products for months or even years, even though they felt ill. People who ate 1,4-DCB products regularly for long periods (months to years) because of its sweet taste developed skin blotches and problems with red blood cells, such as anemia (iron-poor blood). Little information is available about the effects of skin contact with DCBs. 1,4-DCB might cause a burning feeling in your skin if you hold mothballs or toilet-deodorizer blocks against your skin for a long time.

Breathing or eating any of the DCBs caused harmful effects in the liver of laboratory animals. Animal studies also found that 1,2-DCB and 1,4-DCB caused effects in the kidneys and blood, and that 1,3-DCB caused thyroid and pituitary effects. There is no clear evidence that 1,2-DCB and 1,4-DCB impair reproduction or fetal development in animals at levels below those that also cause serious health effects in the mother, although there is an indication that 1,4-DCB can affect development of the nervous system after birth.

Lifetime exposure to 1,4-DCB by breathing or eating induced liver cancer in mice. 1,2-DCB was not carcinogenic in laboratory animals, and 1,3-DCB has not been tested for its potential to cause cancer. The animal studies suggest that 1,4-DCB could play a role in the development of cancer in humans, but we do not definitely know this. The U.S. Department of Health and Human Services (DHHS) has determined that 1,4-DCB might be a human carcinogen. The International Agency for Research on Cancer (IARC) determined that 1,4-DCB is possibly carcinogenic to humans. Both IARC and the EPA concluded that 1,2-DCB and 1,3-DCB are not classifiable as to human carcinogenicity.

More information about how DCBs can affect your health is given in Chapter 3.

1.6 HOW CAN DICHLOROBENZENES AFFECT CHILDREN?

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

Children are exposed to DCBs in many of the same ways adults are. It is possible that mothballs and toilet bowl deodorant blocks containing 1,4-DCB could be played with or accidentally swallowed, especially by young children. Because children tend to be curious about unknown powders and liquids, and because these products might be easily accessible in cabinets, closets, or bathrooms, children could be at a higher risk of exposure to 1,4-DCB than adults.

Children who are exposed to DCBs are likely to exhibit the same effects as adults, although this is not known for certain. Thus, all health problems of DCBs observed in adults are of potential concern in children.

Children can also be exposed to DCBs prenatally, because all three isomers have been detected in placenta samples, as well as through breast feeding. There is no reliable evidence suggesting that DCBs cause birth defects, although animal data raise concern for effects of 1,4-DCB on postnatal development of the nervous system.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO DICHLORO-BENZENES?

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

You and your children could be exposed to 1,4-DCB in your home if you use consumer products that contain 1,4-DCB, such as some toilet bowl cleaners and mothballs. Exposure of children to 1,4-DCB can be minimized by discouraging them from playing with, swallowing, or having skin contact with treated products. These items should be stored out of reach of young children and kept in their original containers to prevent accidental poisonings. Keep your Poison Control Center’s number by the phone.

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

Several tests can be used to show if you have been exposed to DCBs. The most commonly used tests measure their dichlorophenol breakdown products in urine and blood. These tests require special equipment that is not routinely available in a doctor's office, but they can be performed in a special laboratory.

The presence of the dichlorophenol breakdown products in the urine indicates a person has been exposed to DCBs within the previous day or two. For example, detection of 2,5-dichlorophenol in urine is commonly used to determine worker exposure to 1,4-DCB in industrial settings. Another test measures levels of DCBs in your blood, but this is used less often. Neither of these tests can be used to show how high the level of DCB exposure was or to predict whether harmful health effects will follow.

More information about how 1,4-DCB can be measured in exposed people is presented in Chapters 3 and 7.

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

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

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based

on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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

The federal government has taken a number of steps to protect people from excessive exposure to DCBs. EPA has listed 1,2-, 1,3-, and 1,4-DCB as hazardous wastes and subjects them to hazardous waste regulations. EPA has set maximum levels of 600 micrograms (μg) of 1,2-DCB and 75 μg of 1,4-DCB per liter of drinking water. 1,4-DCB is a pesticide registered with EPA, and its manufacturers must provide certain kinds of information to EPA for it to be registered for use as a pesticide. OSHA has set maximum levels of 50 ppm for 1,2-DCB and 75 ppm for 1,4-DCB in workplace air for an 8-hour day, 40-hour workweek.

More information about federal and state regulations regarding DCBs is presented in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information

and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

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

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DICHLOROBENZENES IN THE UNITED STATES

Dichlorobenzenes (DCBs) are chlorinated aromatic compounds that have three isomeric forms. 1,2-DCB is a colorless to pale yellow liquid used primarily as a precursor for 3,4-dichloroaniline herbicides. 1,3-DCB is a colorless liquid used in the production of various herbicides, insecticides, pharmaceuticals, and dyes. 1,4-DCB, the most commercially important dichlorobenzene isomer, is a volatile colorless to white crystalline material with a mothball-like, penetrating odor. It is used as a deodorant for restrooms, for moth control, and in the production of polyphenylene sulfide (PPS) resin.

DCBs are not known to occur naturally in the environment. The primary sources of 1,4-DCB of industrial or commercial origin in the environment are releases from space deodorants and moth repellants into the atmosphere. 1,4-DCB might also be released into water through waste water streams and landfill leachate and to soil through sewage sludge application, disposal of industrial waste, and atmospheric deposition. 1,2- and 1,3-DCBs are expected to be released to the environment during their use in herbicide production or during the use of other products containing these isomers. 1,2-DCB is produced in large quantities as a by-product during the production of 1,4-DCB and can be released into the environment during the disposal of unused supplies.

1,2-, 1,3-, and 1,4-DCB have similar physical and chemical properties, and consequently are expected to have similar environmental fates. DCBs will exist predominantly in the vapor-phase in the atmosphere. They are degraded in the atmosphere by reaction with hydroxyl radicals, with atmospheric lifetimes (theoretically calculated) of about 1 month. The detection of these chemicals in rainwater suggests that atmospheric removal via washout is possible. Depending on soil type, DCBs are expected to be moderately mobile in soil and to volatilize from surface water and soil surfaces to the atmosphere. Volatilization, sorption, biodegradation, and bioaccumulation are likely to be competing processes, with the dominant fate being determined by local environmental conditions.

DCB concentrations in soil, water, and food are generally low in comparison to concentrations in air, indicating that exposure of the general population to DCBs is predominantly by inhalation. Individuals are more likely to be exposed to 1,4-DCB than to the other isomers due to the widespread use of the

1,4-isomer in deodorant and moth repellent products. Measured DCB concentrations in ambient outdoor air generally range from 0.01 to 0.1 ppb for 1,2-DCB, from 0.001 to 0.1 ppb for 1,3-DCB, and from 0.01 to 1 ppb for 1,4-DCB. The average daily adult intakes of 1,2-, 1,3-, and 1,4-DCB from ambient air have been estimated to be about 1.8, 0.8, and 35 μg/day, respectively. The heavy use of products containing 1,4-DCB in homes and other buildings has resulted in higher concentrations of this substance in indoor air compared to concentrations in outdoor air. Measured 1,4-DCB concentrations in indoor air generally range from 0.1 ppb to 100 ppb. Indoor inhalation exposure to 1,2- or 1,3-DCB is not expected to be important since these substances are not used in household and consumer products to the extent of 1,4-DCB. 1,2- and 1,4-DCB have been detected in adipose tissue at concentrations ranging from <0.1 to 38 ppb and from 0.2 to 500 ppb, respectively. 1,4-DCB has been detected in blood samples at concentrations ranging from below 0.04 to 45 ppb, while measured 1,2-DCB concentrations in blood are below 3 ppb.

Children can be exposed to DCBs prenatally, as indicated by the detection of all three isomers in placenta samples, as well as through breast feeding. 1,2-DCB concentrations measured in whole human milk range from 3 to 29 ppb. 1,3- and 1,4-DCB were detected together in whole human milk with mean and maximum concentrations of 6 and 75 ppb, respectively. These isomers were detected in milkfat samples at a mean concentration of 161 ppb and a maximum concentration of 4,180 ppb. 1,2-, 1,3-, and 1,4-DCB measured separately in whole human milk samples had concentrations of 9, <5, and 25 ppb, respectively, while the milk fat of these samples contained 230 ppb of 1,2-DCB and 640 ppb of 1,4-DCB. Children and adults are perhaps at equal risk for exposure to 1,4-DCB since there is no evidence to indicate that children are likely to be exposed to lower amounts of 1,4-DCB from everyday living. While actual exposure reports are limited to a small number of case reports, available evidence suggests that children may be exposed to 1,4-DCB if they eat or play with moth balls or toilet deodorizers.

2.2 SUMMARY OF HEALTH EFFECTS

1,2-Dichlorobenzene. 1,2-DCB is quickly and extensively absorbed through both the gastrointestinal tract and the respiratory tract; studies measuring the absorption of 1,2-DCB following dermal exposure are not available. Following absorption, 1,2-DCB is distributed throughout the body, but tends to be found in greatest levels in the fat, kidney, and liver. 1,2-DCB is initially metabolized by cytochrome P-450 enzymes, specifically P4502E1, to an active epoxide followed by hydrolysis to 2,3-dichlorophenol or 3,4-dichlorophenol. The dichlorophenols may be further oxidized or, more often, be conjugated to glutathione, sulfate, or to form the glucuronide; conjugation occurs extensively, with virtually no

unconjugated metabolites reported in the available studies. Metabolism is believed to occur mainly in the liver, but may occur at lower levels in other tissues, such as the kidney or lung. Elimination of 1,2-DCB from the body is rapid, with the majority of a single dose being removed within the first 75 hours postexposure; elimination occurs primarily in the urine as metabolites.

Information on health effects of 1,2-DCB in humans is essentially limited to observations of respiratory tract and eye irritation in workers chronically exposed to the vapor. The potential for inhaled 1,2-DCB to cause respiratory tract effects is also shown by the induction of nasal olfactory lesions in an acute-duration study in mice. This effect occurred at concentrations similar to or below the lowest exposure levels that caused systemic effects in rats, mice, and guinea pigs in other acute and intermediate-duration inhalation studies. No intermediate-duration studies examined the nasal cavity, indicating that a critical effect for longer-term inhalation exposures cannot be identified. The liver is the primary systemic target of toxicity in animals exposed to 1,2-DCB. Acute-, intermediate,- and chronic-duration inhalation and oral studies clearly identify the liver as a sensitive target of oral exposure, inducing increases in liver weight at low levels of exposure and histological changes such as cloudy swelling and centrilobular degeneration and necrosis at higher levels in rats and mice.

Data on the possible effects of 1,2-DCB on reproductive or developmental end points in humans are not available. Studies by both the oral and inhalation routes of exposure failed to find effects of 1,2-DCB on histology of reproductive organs or indices of reproduction in rats and mice. Similarly, limited available data suggest that inhalation and oral exposure to 1,2-DCB do not significantly affect prenatal development in rats or rabbits.

Data on the possible carcinogenic effects of 1,2-DCB in humans are not available. Exposure to 1,2-DCB by the oral route has not been shown to cause an increase in tumor formation following lifetime exposure in rats or mice. The potential carcinogenic effects of 1,2-DCB by other routes of exposure have not been evaluated. EPA determined that 1,2-DCB is not classifiable as to human carcinogenicity and categorized it in cancer weight-of-evidence Group D. The International Agency for Research on Cancer (IARC) similarly determined that 1,2-DCB is not classifiable as to carcinogenicity to humans (Group 3).

A more detailed discussion of the hepatic and respiratory effects associated with 1,2-DCB exposure follows. The reader is referred to Section 2.2, Discussion of Health Effects by Route of Exposure, for additional information on these and other health effects.

Hepatic Effects. Data on the hepatic effects of 1,2-DCB in exposed humans are not available for any exposure route. The liver is the primary target in animals orally exposed to 1,2-DCB, generally resulting in centrilobular damage in acute- and subchronic-duration studies. A single exposure to 1,500 mg/kg in rats caused lethal central necrosis. In rats exposed to 455 mg/kg/day for 15 days, severe liver damage, characterized by intense necrosis and fatty changes and porphyria, were reported. Similarly, rats exposed to 300 mg/kg/day for 10 days showed hepatic necrosis of slight severity and increased serum alanine aminotransferase (ALT). However, an acute (14-day) study by the National Toxicology Program showed no hepatic effects in male or female rats given doses as high as 500 or 1,000 mg/kg/day for 14 consecutive days. The inconsistency between these findings might be due to a small number of animals in the14-day study and a low incidence and severity of lesions in the 10-day study. Centrilobular liver effects similar to those reported in the acute studies were found in several intermediate-duration studies in rats and mice, occurring in rats exposed to 188 mg/kg/day for 138 doses, rats exposed to 400 mg/kg/day for 90 days, rats exposed to 250 mg/kg/day or greater for 13 weeks, and mice exposed to 250 mg/kg/day for 13 weeks. A chronic study in rats and mice found no nonneoplastic liver effects in either sex of either species, even at exposures up to 120 mg/kg/day, suggesting that the nonneoplastic hepatic effects of 1,2-DCB may have a threshold, which might fall between 120 and 188 mg/kg/day.

Respiratory Tract Effects. Periodic industrial hygiene surveys and medical examinations were conducted in a plant where an unreported number of men were exposed to 1,2-DCB at an average level of 15 ppm (range, 1–44 ppm) for an unreported duration; no nasal or eye irritation was attributable to exposure. Additionally, the study author noted that the researchers detected 1,2-DCB odor at a concentration of 50 ppm without eye or nasal irritation during repeated vapor inhalation experiments on animals. An earlier source reported that occupational exposure to 100 ppm of 1,2-DCB caused irritation of the eyes and respiratory passages of exposed humans. Data on the effects of 1,2-DCB on the respiratory tract in humans following oral or dermal exposure are not available.

In male mice exposed to 1,2-DCB in mean concentrations of 0, 64, or 163 ppm for 6 hours/day, 5 days/week for 4, 9, or 14 days, histopathologic lesions were observed in the olfactory epithelium of the nasal cavity at ≥64 ppm. The olfactory epithelial lesions were graded as very severe following the 4-day exposure and moderate after the 14 day exposure, indicating to the study authors that repair may occur despite continued exposure. The more severe cases were characterized by a complete loss of olfactory epithelium, which left only partially denuded basement membrane. No histological alterations were observed in the respiratory epithelium of the nasal cavity, or in the trachea or lungs. No effects on

respiratory tract tissues were reported in intermediate- or chronic-duration inhalation studies in animals; however, in most cases, evaluation of nasal tissues was not conducted.

1,3-Dichlorobenzene. Data on the absorption of 1,3-DCB in humans and animals are not available for any route of exposure; however, absorption of the compound can be inferred from studies that have detected 1,3-DCB or metabolites in the breast milk, blood, and fat of humans and in the bile and urine of exposed animals. Distribution is believed to be similar to the other DCB isomers, but data demonstrating this are not currently available. Similar to the other DCB isomers, 1,3-DCB is initially metabolized by cytochrome P 450 enzymes, followed by extensive conjugation, primarily to glutathione. 1,3-DCB is eliminated mainly in the urine, similar to the other DCB isomers.

Studies on the toxic effects of 1,3-DCB in humans are not available. No studies evaluating the toxicity of 1,3-DCB following dermal or inhalation exposure in animals were located. Information on the oral toxicity of 1,3-DCB in animals is available from one 90-day systemic toxicity study and one developmental toxicity study. The intermediate-duration study found effects in the thyroid, pituitary, and liver of rats, with thyroid lesions occurring at dose levels lower than those inducing pituitary and liver effects. The information on the developmental toxicity study of 1,3-DCB is from a gavage study reported without details as an abstract, which reported no treatment-related effects on prenatal development in rats. Reproductive function and carcinogenicity have not been evaluated in humans or animals exposed to 1,3-DCB. EPA determined that 1,3-DCB is not classifiable as to human carcinogenicity and categorized it in cancer weight-of-evidence Group D. IARC similarly determined that 1,3-DCB is not classifiable as to carcinogenicity to humans (Group 3).

A more detailed discussion of the endocrine and hepatic effects associated with 1,3-DCB exposure follows. The reader is referred to Section 2.2, Discussion of Health Effects by Route of Exposure, for additional information on these and other health effects.

Endocrine Effects. In a 90-day study in rats given 0, 9, 37, 147, or 588 mg/kg/day, the most sensitive reported effects were on the pituitary and thyroid glands. Histologically, depletion of colloid density in the thyroid, characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar, was increased in a dose-related manner in males exposed to ≥9 mg/kg/day, and in females exposed to ≥37 mg/kg/day. The pituitary glands of males exposed to 1,3-DCB showed cytoplasmic vacuolization of the pars distalis in all exposed groups, but the incidence was statistically significant only in animals exposed to ≥147 mg/kg/day. Increases in serum cholesterol in males at

≥9 mg/kg/day and females at ≥37 mg/kg/day, and serum calcium in both sexes at ≥37 mg/kg/day were also believed by the authors to be related to effects on endocrine end points, possibly reflecting a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs.

Hepatic Effects. In male and female rats exposed by gavage to up to 735 mg/kg/day for 10 days, hepatic effects included significantly increased relative liver weight in males at ≥147 mg/kg/day and females at ≥368 mg/kg/day, and altered histopathology at ≥368 mg/kg/day in both sexes. The main hepatic histological change was dose-related centrolobular hepatocellular degeneration, characterized by varying degrees of cytoplasmic vacuolization and swelling with intact membranes. Other hepatic alterations included hepatocellular necrosis that was sporadically noted in animals exposed to ≥147 mg/kg/day; this change was usually minimal to mild, and tended to increase in incidence and severity in males in a dose-related manner. In a 90-day study of 1,3-DCB toxicity, rats of both sexes were exposed by gavage to up to 588 mg/kg/day. Relative liver weights were increased in both sexes at ≥147 mg/kg/day. Dose-related increases in histological lesions, including inflammation, hepatocellular alterations, and hepatocellular necrosis were reported at doses of ≥147 mg/kg/day. Other statistically significant liver-associated effects included significantly increased serum aspartate aminotransferase (AST) levels (90–100% higher than controls) in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day, but whether these changes were due to an effect on the liver or an endocrine effect is not clear. Serum lactate dehydrogenase (LDH) levels were also reduced in males at ≥9 mg/kg/day, but the biological significance of a decrease in liver enzymes is unclear.

1,4-Dichlorobenzene. Following inhalation or oral exposure, absorption of 1,4-DCB is rapid and complete. Data on the absorption of 1,4-DCB following dermal exposure are not available; however, absorption is believed to be very low, based on a very high (>6 g/kg) dermal LD_{50} for 1,4-DCB in rats, and on a lack of systemic effects in humans who held solid 1,4-DCB in their hands. Similar to the other dichlorobenzene isomers, 1,4-DCB is distributed throughout the body, but tends to be found in greatest levels in fat, liver, and kidney. Metabolism of 1,4-DCB is similar to that of 1,2-DCB, with an initial oxidation to an epoxide, followed by hydrolysis to 2,5-dichlorophenol. Extensive phase II metabolism occurs subsequently, with eliminated metabolites found mainly as the sulfate, glucuronide, or mercapturic acid. 1,4-DCB is eliminated almost exclusively in the urine, primarily as conjugates of 2,5-dichlorophenol.

Information on the health effects of 1,4-DCB in humans is available from limited observations in exposed workers and case reports. Workers who were chronically exposed to 1,4-DCB vapor experienced irritation of the nose and eyes and case reports of people who inhaled or ingested 1,4-DCB suggest that the liver, nervous system, and hematopoietic system are systemic targets in humans. The available limited information on these systemic effects in humans is consistent with findings in animals exposed to 1,4-DCB.

The acute, intermediate,- and chronic-duration toxicity of 1,4-DCB in animals has been evaluated in a number of studies, predominantly in rats and mice. The respiratory tract is a target of inhaled 1,4-DCB as shown by histopathological changes in the lungs of acutely exposed rats and guinea pigs and nasal olfactory epithelium of chronically exposed rats and mice. Liver and kidney effects are the best studied and most consistently observed effects of inhalation and oral exposure. There is a general pattern in which increased liver weight and hepatocellular hypertrophy are predominant effects at exposure levels below those inducing more serious histopathological changes in the liver (e.g., congestion, fatty degeneration, focal necrosis) and clinical signs of toxicity in the respiratory tract (e.g., nose and eye irritation following inhalation exposure) and nervous system (e.g., tremors and salivation). Exposure of male rats to 1,4-DCB, but not female rats or either sex of other species, causes development of renal lesions that have been shown to be the result of interaction with the protein $\alpha_{2\mu}$-globulin, a mechanism specific to male rats and not relevant to humans. There are a few reports of effects on the hematologic system, adrenal gland, and thyroid, but these occurred at inhalation or oral exposure levels similar to or higher than those causing liver and kidney effects. Chronic inhalation exposure to 1,4-DCB induced nasal olfactory epithelial lesions in rats at concentrations below those causing liver effects.

Data on the effects of 1,4-DCB on reproductive end points in humans are not available. Oral or inhalation exposure to 1,4-DCB has not been demonstrated to produce treatment-related adverse changes in reproductive tissue histology or on reproductive end points in animals. Two-generation inhalation and oral studies in rats found that 1,4-DCB did not affect reproductive performance but induced postnatal toxicity in F_1 and F_2 offspring, including reductions in survival on day 4, body weight gain, and neurobehavioral performance at doses similar to or lower than those inducing liver effects in intermediate-duration systemic toxicity studies. No teratogenic effects were induced in rats by inhalation or oral exposure to 1,4-DCB, although indications of fetotoxicity (e.g., extra ribs) occurred at levels that were maternally toxic.

1,4-DCB is carcinogenic in animals following chronic inhalation and oral exposure. Inhalation and oral lifetime studies found liver tumors in male and female mice but not in rats of either sex. Chronic oral exposure also induced renal tubular cell adenocarcinomas in male rats, but these appear to be associated with male rat-specific $\alpha_{2\mu}$-globulin nephropathy and not relevant to carcinogenicity in humans. IARC determined that 1,4-DCB is possibly carcinogenic to humans (Group 2B). The Department of Health and Human Services (DHHS) concluded that 1,4-DCB is reasonably anticipated to be a human carcinogen.

A more detailed discussion of the hepatic, respiratory, developmental, and carcinogenic effects associated with 1,4-DCB exposure follows. The reader is referred to Section 2.2, Discussion of Health Effects by Route of Exposure, for additional information on these effects and other health effects.

Hepatic Effects. In two human fatalities believed to be caused by 1,4-DCB inhalation, the subjects died of massive hepatic necrosis; the exposure concentrations are not known. A 3 year-old child who had been playing with crystals containing 1,4-DCB for 4–5 days was jaundiced with pale mucous membranes, indicative of liver damage.

Many animal studies by both the oral and inhalation routes have confirmed the liver as a sensitive target for 1,4-DCB toxicity. Inhaled exposure concentrations of 158–211 ppm, at exposure durations from 2 weeks to 7 months, resulted in increased liver weights, cloudy swelling of the liver, and, at higher exposure levels, centrilobular hypercellular hypertrophy and necrosis. Exposure to 270 ppm for 13 weeks caused increased liver weight in rats and mice and hepatocellular hypertrophy and increased serum enzymes in mice. Exposure to 538 ppm for 10 weeks, and throughout mating and gestation for females, resulted in hepatocellular hypertrophy and increased liver weights in both the parental (F_0) generation and the F_1 generation offspring. In chronic inhalation studies in rats and mice, no effects were seen in either sex of either species at 75 ppm, but at 300 ppm, histological changes in the lung were seen in male mice, but not in female mice or in either sex of rats. Acute oral studies have demonstrated hepatic effects (increased liver weight) at concentrations as low as 300 mg/kg in rats, with higher concentrations resulting in increased liver cell proliferation and vacuolated and/or basophilic cytoplasm of centrilobular cells. Similar hepatic effects occurred in mice orally exposed to 300 mg/kg/day for 1 week. In rats exposed to 1,4-DCB for 13 weeks, increased relative liver weight was seen at ≥75 mg/kg/day, with centrilobular hypertrophy present at 300 mg/kg/day (Lake et al. 1997), and necrosis reported at 1,200 mg/kg/day (NTP 1987); oral studies in mice have reported similar effects (NTP 1987). A study of 1,4-DCB in male and female Beagle dogs found that oral exposure to 50 or 75 mg/kg/day caused increased serum levels of liver enzymes, increased liver weights, hepatocellular hypertrophy, pigment

deposition, and hepatic portal inflammation after 6–12 months. In the only chronic-duration (2-year) oral study of 1,4-DCB toxicity, no effects were seen in either sex of rats exposed to up to 300 mg/kg/day, while both sexes of mice showed significant, dose-related increases in hepatocellular degeneration, starting at 300 mg/kg/day.

Respiratory Tract Effects. A case of pulmonary granulomatosis was reported to have occurred in a 53-year-old woman who for 12–15 years had been inhaling 1,4-DCB crystals that were scattered on a weekly basis on the carpets and furniture of her home. A lung biopsy revealed the presence of 1,4-DCB crystals with the surrounding lung parenchyma being distorted by fibrosis, thickening of the alveolar walls, and marked infiltrates of lymphocytes and mononuclear phagocytes. These effects are most likely related to the physical interaction of 1,4-DCB crystals (or any crystals when inhaled) with lung tissue, rather than to chemical toxicity. A health survey of 58 men occupationally exposed to 1,4-DCB for 8 hours/day, 5 days/week for 8 months to 25 years (average, 4.75 years) found the odor to be faint at 15–30 ppm and strong at 30–60 ppm, with painful irritation of the nose and eyes usually occurring at concentrations ranging from 80 to 160 ppm. At levels >160 ppm, the air was considered not breathable for unacclimated persons.

An evaluation of 953 adult participants in the Third National Health and Nutrition Examination Survey of the general U.S. population found statistically significant inverse associations between blood levels of 1,4-DCB and two measures of pulmonary function. When compared with subjects in the lowest decile of 1,4-DCB blood concentration (0.10 ppb), subjects in the highest decile (>4.40 ppb) had decrements of -153 mL in forced expiratory volume in 1 second (FEV1) and -346 mL/second in maximum mid-expiratory flow rate (MMEFR). There were no significant associations with forced vital capacity (FVC) or peak expiratory flow rate (PEFR). Although it is unclear whether the observed decrements in FEV1 and MMEFR are biologically meaningful, and other studies investigating effects of 1,4-DCB on lung function are not available, the findings suggest that exposure to 1,4-DCB may possibly contribute to decreases in lung function.

Pulmonary effects (interstitial edema, congestion, and alveolar hemorrhage) were observed in rats and guinea pigs following intermittent exposure to 175 ppm of 1,4-DCB for 16 days. The experimental design and report of this study have a number of deficiencies, such that the observations provide only qualitative evidence of exposure-related acute respiratory effects. Support for the respiratory tract as a target for inhaled 1,4-DCB in animals is provided by the induction of nasal lesions in rats and mice chronically exposed to 1,4-DCB for 6 hours/day, 5 days/week for 2 years. An increased incidence of

histological changes of the nasal olfactory epithelium occurred in female rats exposed to 75 or 300 ppm, and male rats and female mice exposed to 300 ppm. In rats treated with 1,200 or 1,500 mg/kg/day or greater by gavage for 13 weeks, epithelial necrosis of the nasal turbinates was reported; similar effects were not seen in mice exposed by gavage to up to 1,800 mg/kg/day, or in rats or mice exposed by gavage for 2 years to up to 600 mg/kg/day.

Developmental Effects. A 21-year-old woman who had eaten 1–2 blocks of 1,4-DCB toilet freshener per week for the first 38 weeks of pregnancy gave birth to an apparently normal child. In a 2-generation study of the effects of inhaled 1,4-DCB on reproduction and development, the number of pups that died during the perinatal period was increased, and the body weights at postnatal day 0 and 28 were significantly decreased, in animals exposed to 538 ppm; exposures to 66 or 211 ppm had no effect on developmental end points. In rabbits exposed to 300 ppm, but not those exposed to 800 ppm, there was a significant increase in the number of resorptions and the percentages of resorbed implantations per litter; the fact that the effect did not occur in the rabbits exposed to the higher exposure level suggests that it was not treatment-related. A 2-generation oral study in rats found toxicity in the offspring at doses ≥90 mg/kg/day; effects included reduced birth weight in F_1 pups, increased mortality on postnatal day 4 in F_1 and F_2 pups, clinical manifestations of dry and scaly skin (until approximately postnatal day 7) in F_1 and F_2 pups, and reduced neurobehavioral performance (draw-up reflex evaluated at weaning) in F_2 pups. No exposure-related changes occurred at 30 mg/kg/day. Other evaluations of developmental effects of 1,4-DCB following oral exposure have been negative.

Cancer. Data on the carcinogenic effects of 1,4-DCB in humans are not available. 1,4-DCB has been shown to be carcinogenic in chronic animal studies by both the inhalation and oral routes. Following lifetime inhalation exposure, a dose-related increase in hepatocellular adenomas and carcinomas was observed in mice of both sexes, whereas incidences of liver or other tumors were not increased in rats. Following lifetime oral exposure, hepatic tumors (hepatocellular adenomas and carcinomas and histiocytic sarcomas) were increased in mice of both sexes, but not in either sex of rats. The oral bioassay also found that the male rats exposed to 1,4-DCB developed renal tubular cell adenocarcinomas, but these are believed to be the result of interaction with $\alpha_{2\mu}$-globulin, a renal protein not present in humans. Data on the possible carcinogenic effects of 1,4-DCB following dermal exposure are not available.

2.3 MINIMAL RISK LEVELS (MRLs)

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1994k), 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-Dichlorobenzene

Acute-Duration Exposure. No MRL was derived for acute-duration inhalation exposure to 1,2-DCB due to insufficient data. No information was located regarding the acute inhalation toxicity of 1,2-DCB in humans. The nasal cavity was a target of acute inhalation in animals as shown by a study in which male mice were exposed to 64 or 163 ppm of 1,2-DCB for 6 hours/day, 5 days/week for 4, 9, or 14 days (Zissu 1995). Histological examinations of the upper and lower respiratory tracts found that nasal olfactory epithelial lesions occurred at both levels of exposure. The nasal lesions were graded as very severe following the 4 day exposure and moderate after the 14 day exposure, suggesting to the study authors that some tissue repair might have occurred despite continued exposure. The more severe cases were characterized by a complete loss of olfactory epithelium, which left only the partially denuded basement membrane. No histological alterations were observed in the respiratory epithelium of the nasal cavity, or in the trachea or lungs. Nonrespiratory tissues were not evaluated in this study.

Acute systemic effects of inhaled 1,2-DCB include histopathology in the liver (marked centrilobular necrosis) and kidneys (cloudy swelling of tubular epithelium) of rats exposed to 977 ppm for 1 hour (Hollingsworth et al. 1958), but not to 539 ppm for 3 or 6.5 hours (Hollingsworth et al. 1958) or 322 ppm for 6 hours/day for 10 days (DuPont 1982). Maternal body weight gain was decreased in rats and rabbits that were exposed to 100, 200, or 400 ppm of 1,2-DCB for 6 hours/day on days 6–15 (rats) or 6–18 (rabbits) of gestation (Hayes et al. 1985). No prenatal developmental toxicity was observed in the rabbits, although skeletal variations (delayed ossification of cervical vertebral centra) occurred in fetuses of rats at 400 ppm, indicating that developmental effects occurred in rats at concentrations that also caused maternal toxicity. Based on these findings, a lowest-observed-adverse-effect level (LOAEL) of 100 ppm for systemic toxicity and 400 ppm for developmental toxicity are identified.

The nasal histopathology findings in mice show that the upper respiratory tract is a sensitive target for acute inhalation exposure to 1,2-DCB, as serious olfactory lesions occurred at exposure concentrations below those that caused systemic or developmental effects in rats and rabbits. The 64 ppm LOAEL for severe nasal olfactory lesions precludes derivation of an acute inhalation MRL for 1,2-DCB because: (1) a no-observed-adverse-effect level (NOAEL) for nasal lesions was not determined, (2) no other animal studies tested exposure levels below 100 ppm or evaluated the nasal cavity, and (3) it is not ATSDR's practice to derive MRLs based on serious LOAELs.

Intermediate-Duration Exposure. No intermediate-duration inhalation MRL was derived for 1,2-DCB due to insufficient data. Information on the toxicity of intermediate-duration inhalation exposures to 1,2-DCB is limited to the findings of a multispecies intermediate study (Hollingsworth et al. 1958) and a 2-generation reproduction study in rats (Bio/dynamics 1989). In the intermediate study, rats and guinea pigs were exposed to 49 or 93 ppm for 7 hours/day, 5 days/week for 6–7 months (Hollingsworth et al. 1958). Mice were similarly exposed to 49 ppm only, and rabbits and monkeys were similarly exposed to 93 ppm only, although the rabbit and monkey data are compromised by small numbers of animals (two rabbits/sex and two female monkeys). No compound-related histopathological or other changes occurred in any of the animals exposed to 49 ppm. The only remarkable findings at 93 ppm were statistically significant decreases in final body weight (8.9% less than controls) in male rats and absolute spleen weight (20% less than controls) in male guinea pigs, indicating that the NOAEL and LOAEL for systemic effects are 49 and 93 ppm, respectively. In the reproductive toxicity study, male and female rats were exposed to 50, 150, or 394 ppm of 1,2-DCB for 6 hours/day, 7 days/week for 10 weeks before mating and subsequently through the F_1 generation (Bio/dynamics 1989). $\alpha_{2\mu}$-Globulin-

related renal changes were found in adult males of both generations at all levels of exposure, but these effects are specific to male rats and are not relevant to humans. Decreased body weight gain, increased absolute and relative liver weights, and centrilobular hepatocyte hypertrophy occurred in adult rats of both sexes and generations at ≥150 ppm, indicating that the NOAEL and LOAEL for systemic effects are 50 and 150 ppm. There were no effects on reproduction in either generation, indicating that the NOAEL for reproductive toxicity is 394 ppm. As discussed in the acute inhalation MRL section, a NOAEL of 200 ppm and a LOAEL of 400 ppm were found for developmental toxicity (skeletal variations) in rats (Hayes et al. 1985).

As discussed above, NOAELs of 49–50 ppm and LOAELs of 93–150 ppm are identified for systemic effects in intermediate-duration inhalation studies of 1,2-DCB in rats and guinea pigs (Bio/dynamics 1989; Hollingsworth et al. 1958). Neither of these studies evaluated possible effects in the nasal cavity, a known sensitive target of 1,2-DCB based on acute data. As indicated in the acute inhalation MRL section, 64 ppm was a serious LOAEL for nasal olfactory lesions in rats intermittently exposed to 1,2-DCB for 4–14 days (Zissu 1995). Derivation of an intermediate-duration MRL for 1,2-DCB is precluded because the 64 ppm serious LOAEL for acute exposure is lower than the available intermediate-duration LOAELs for systemic and developmental effects.

Chronic-Duration Exposure. No MRL was derived for chronic-duration inhalation exposure to 1,2-DCB due to insufficient data. The available information consists of two limited human reports. Workers who were exposed to concentrations of 1,2-DCB ranging from 1 to 44 ppm (average 15 ppm) for unreported durations did not experience eye or nasal irritation, or show any changes in standard blood and urine indices, as determined by periodic occupational health examinations (Hollingsworth et al. 1958). 1,2-DCB also did not cause eye or nasal irritation in workers exposed to approximately 50 ppm (researchers exposed during the conduct of inhalation studies in animals), although the odor was perceptible at this level (Hollingsworth et al. 1958). Occupational exposure to higher concentrations of 100 ppm 1,2-DCB was reported to be irritating to the eyes and respiratory passages (Elkins 1950). The lack of adequate exposure-response data and any additional information in these reports, as well as a lack of chronic toxicity data in animals, precludes derivation of a chronic inhalation MRL.

1,3-Dichlorobenzene

No MRLs were derived for inhalation exposure to 1,3-DCB due to a lack of acute-, intermediate-, and chronic-duration inhalation studies.

1,4-Dichlorobenzene

Acute-Duration Exposure.

- An MRL of 2 ppm has been derived for acute-duration (≤14 days) inhalation exposure to 1,4-DCB.

A limited amount of information is available on the toxicity of inhaled 1,4-DCB in humans. Case reports of people who inhaled 1,4-DCB provide indications that the liver and nervous system are systemic targets of inhalation toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-DCB was the only factor associated with the effects (Cotter 1953; Miyai et al. 1988; Reygagne et al. 1992).

Observations in workers who were occupationally exposed to 1,4-DCB for 8 hours/day, 5 days/week for an average of 4.75 years (range from 8 months to 25 years) provide information relevant to acute inhalation exposures. The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. The odor and irritation effects are considered to be good acute warning properties that are expected prevent excessive exposures, although the industrial experience indicates that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor (Hollingsworth et al. 1956). Periodic occupational health examinations showed no cataracts or any other lens changes in the eyes, or effects on clinical indices (red blood cell count, total and differential white blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, blood urea nitrogen, sedimentation rate, or urinalysis) attributable to exposure.

Information on effects of acute-duration inhalation exposure to 1,4-DCB in animals is available from short-term systemic toxicity studies in rats and guinea pigs (Hollingsworth et al. 1956), a male reproduction study rats (Anderson and Hodge 1976), and developmental toxicity studies in rats and rabbits (Hayes et al. 1985; Hodge et al. 1977). In the systemic toxicity study, five rats of each sex and five guinea pigs of each sex were exposed to 173 ppm of 1,4-DCB for 7 hours/day, 5 days/week for 16 days (Hollingsworth et al. 1956). Mild histological effects of interstitial edema, congestion, and alveolar hemorrhage were observed in the lungs of male rats and female guinea pigs. The experimental design and report of this study have a number of deficiencies, such that reported observations provide

only qualitative evidence of exposure-related respiratory effects. In the reproduction study (a dominant lethal test), a NOAEL of 450 ppm was identified for reproductive performance in male mice that were exposed for 6 hours/day for 5 days prior to weekly mating with unexposed females for 8 weeks (Anderson and Hodge 1976). No maternal or developmental toxicity occurred in rats that were exposed to 75–500 ppm for 6 hours/day on days 6–15 of gestation (Hodge et al. 1977), indicating that the highest NOAEL for reproductive effects in rats is 500 ppm. A developmental study in which rabbits were exposed to 100–800 ppm for 6 hours/day on gestation days 6–18 found evidence of fetotoxicity (a minor variation of the circulatory system) only at 800 ppm, which was also maternally toxic as shown by body weight loss early in gestation (Hayes et al. 1985), indicating that 800 ppm is a LOAEL for maternal and developmental effects in rabbits.

The lung is the target of concern for inhaled 1,4-DCB in rats and guinea pigs acutely exposed to 173 ppm (Hollingsworth et al. 1956) because the only effects observed in the acute reproductive and developmental studies were indications of maternal and fetotoxicity in rabbits at a much higher levels of 800 ppm (Hayes et al. 1985). Support for the respiratory tract as a sensitive target for 1,4-DCB vapor in animals is provided by the induction of nasal lesions in rats intermittently exposed to levels as low as 75 ppm for 104 weeks in the study used to derive the chronic inhalation MRL for 1,4-DCB (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Additionally, the animal data are consistent with the human experience indicating that occupational exposure to 1,4-DCB causes painful nose and eye irritation in the range of 50–160 ppm (Hollingsworth et al. 1956). The current Threshold Limit Value-Time Weighted Average (TLV-TWA) for 1,4-DCB of 10 ppm, which is intended to minimize the potential for eye irritation in exposed workers (ACGIH 2001), is largely based on the human findings of Hollingsworth et al. (1956).

As discussed above, eye and nose irritation are critical effects of acute and longer-term inhalation exposures to 1,4-DCB in humans. Because odor detection is a warning property expected to prevent irritation caused by 1,4 DCB (Hollingsworth et al. 1956), the highest level at which an odor was detected that was simultaneously without irritant effects, 30 ppm, was designated a minimal LOAEL for irritation for the purposes of derivation of the MRL; the 15 ppm level was therefore designated a NOAEL for irritant effects. Using the NOAEL of 15 ppm for eye and nose irritation in humans, and applying a total uncertainty factor of 10 (for individual variability), an MRL of 2 ppm was derived for acute inhalation exposure to 1,4-DCB.

Intermediate-Duration Exposure.

- An MRL of 0.2 ppm has been derived for intermediate-duration (15–364 days) inhalation exposure to 1,4-DCB.

A limited amount of information is available on the intermediate-duration toxicity of inhaled 1,4-DCB in humans. Case reports of people who inhaled 1,4-DCB over periods of months provide indications that the liver and nervous system are systemic targets of inhalation toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-DCB was the only factor associated with the effects (Cotter 1953; Miyai et al. 1988; Reygagne et al. 1992).

Information on effects of intermediate-duration inhalation exposure to 1,4-DCB in animals is available from 4–7-month toxicity studies in rats, mice, guinea pigs, rabbits, and monkeys (Hollingsworth et al. 1956), a 13-week toxicity study in rats and mice (Aiso et al. 2005a), and a 2-generation reproductive/ developmental toxicity study in rats (Tyl and Neeper-Bradley 1989). These studies show that hepatic effects increase in severity with increasing level of exposure, ranging from increased liver weight at low levels to degenerative and necrotic changes at higher concentrations, and identify the liver as the most sensitive target of intermediate-duration inhalation of 1,4-DCB. The lowest reliable hepatic effect levels are identified in the 13-week and 2-generation studies, as discussed below.

In the 13-week study, groups of 10 male and 10 female F344 rats and 10 male and 10 female BDF_1 mice were chamber-exposed to 1,4-DCB vapor (>99.9% pure) at concentrations of 0, 25, 55, 120, 270, or 600 ppm for 6 hours/day, 5 days/week for 13 weeks (Aiso et al. 2005a). End points evaluated during the study included clinical signs (daily) and body weight and food consumption (weekly). End points evaluated at the end of the 13-week exposure period included hematology (red blood cells [RBC], hemoglobin [Hb], Hematocrit [Hct], mean corpuscular volume [MCV], mean corpuscular hemogloblin [MCH]), blood biochemistry (total protein, albumin, total cholesterol, triglyceride, phospholipid, AST, ALT, alkaline phosphatase, blood urea nitrogen [BUN], creatine), organ weights, and histopathology. The histological examinations were comprehensive and included the nasal cavity, in accordance with OECD test guidelines for a 90-day inhalation study (Aiso 2005; OECD 1981).

There were no exposure-related effects on survival, clinical signs, or body weight gain in the rats (Aiso et al. 2005a). Hematological changes suggestive of microcytic anemia occurred in male rats, including significantly decreased RBC count and hemoglobin concentration at ≥120 ppm, hematocrit at ≥270 ppm,

and MCV and MCH at 600 ppm. Serum biochemical changes included significant increases in total protein in both sexes at 600 ppm, albumin in females at ≥270 ppm and males at 600 ppm, and total cholesterol and phospholipid in males at ≥270 ppm and females at 600 ppm, and significant decreases in triglycerides in males at 600 ppm, AST in both sexes at 600 ppm, and ALT and AP in males at ≥270 ppm. The biological significance of decreases in serum levels of liver enzymes is unclear. Organ weight changes included >10% increases in absolute and relative weights of liver in males at ≥270 ppm and females at 600 ppm, kidneys in males at ≥270 ppm, and spleen in males at 600 ppm. Histological effects included significantly increased incidences of centrilobular hepatocellular hypertrophy in the liver in male rats at 600 ppm and kidney lesions indicative of $\alpha_{2\mu}$-globulin nephropathy in male rats at ≥270 ppm. There were no histopathological changes in hematopoietic tissues, suggesting that the anemia in the male rats was secondary to $\alpha_{2\mu}$-globulin nephropathy-related effects on erythropoietin synthesis in the renal tubules.

There were no exposure-related effects on survival, clinical signs, or body weight gain in the mice (Aiso et al. 2005a). Organ weight changes in the mice included >10% increases in liver weight in males at ≥270 ppm (relative) and 600 ppm (absolute) and females at 600 ppm (absolute and relative); relative liver weights were 9.7, 9.7, 10.1, 23.9, and 62.6% higher than controls in the low- to high-dose males. There were no significant hematological changes in either sex. Serum ALT levels were significantly increased in males at ≥270 ppm (18.2, 9.1, 18.2, 54.5 and 164% higher than controls in the low- to high-dose groups). Other serum biochemical changes included significant increases in ALT in females at 600 ppm, AST in males at 600 ppm, and total cholesterol and total protein in both sexes at 600 ppm. Histological examinations showed significantly increased incidences of centrilobular hepatocellular hypertrophy in male mice at ≥270 ppm and female mice at 600 ppm; incidences in the control to high dose males were 0/10, 0/10, 0/10, 0/10, 10/10, and 10/10. Affected hepatocytes were characterized by cell enlargement, varying nuclear size and shape, and coarse chromatin and inclusion bodies in the nucleus; the severity of these lesions was rated as slight at 270 ppm (males) and moderate at 600 ppm (both sexes). The moderate hepatocellular hypertrophy in the 600 ppm male mice was accompanied by single cell necrosis (1/10) and focal liver necrosis (2/10).

The lowest effect level in the 13-week study (Aiso et al. 2005a) study is 270 ppm based on the kidney and hematological effects in male rats and liver effects in rats and mice. The kidney and hematological effects are consistent with $\alpha_{2\mu}$-globulin nephropathy, which is specific to male rats and not relevant to humans. The mice were more sensitive to the liver effects of 1,4-DCB than the rats because the only hepatic change in the 270 ppm rats was increased liver weight, whereas hepatocellular hypertrophy and

increased serum ALT occurred in addition to increased liver weight in the 270 ppm mice. Additionally, at the next highest tested level of 600 ppm, the mice had nuclear changes and evidence of necrosis in the hypertrophic hepatocytes, and increased serum AST as well as ALT, whereas none of these indicators of hepatocellular damage occurred in the rats. Based on increased relative liver weight (>10%) in both species and histological and serum enzyme changes in the mice, this study identified a NOAEL of 120 ppm and a LOAEL of 270 ppm for hepatic effects.

In the two-generation study, groups of 28 Sprague-Dawley rats of each sex were exposed to actual mean 1,4-DCB concentrations of 0, 66, 211, and 538 ppm (Tyl and Neeper-Bradley 1989). Additional groups of 10 females were similarly exposed for 10 weeks in a satellite study. The animals in the main study were paired within groups for a 3 week mating period to produce the F_1 generation. Main study males that did not successfully mate in the first 10 days of the mating period were paired with the satellite females for 10 days. Main study females that did not successfully mate during the first 10 days of the mating period were paired with proven males for the remaining 11 days of the mating period. Exposures of the main study F_0 females were continued throughout the mating period and the first 19 days of gestation, discontinued from gestation day 20 through postnatal day 4, and then resumed until sacrifice at weaning on postnatal day 28. Exposures of the satellite F_0 females were continued through mating until sacrifice on gestation day 15. Exposures of the F_0 males continued until sacrificed at the end of the study and satellite mating periods. Groups of 28 F_1 weanlings/sex and satellite groups of 10 F_1 female weanlings were exposed for 11 weeks and mated as described above to produce the F_2 generation. Additionally, 20 F_1 weanlings/sex from the control and high exposure groups served as recovery animals that were observed without exposure for 5 weeks prior to sacrifice. Complete necropsies were performed on all F_0 and F_1 adult (parental) animals, F_1 recovery animals, F_1 weanlings not used in the rest of the study, and F_2 weanlings, and histology was evaluated in the F_0 and F_1 parental animals. Histological examinations were conducted on the liver and kidneys in all groups and on selected other tissues (pituitary, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, prostate, and tissues with gross lesions) in the control and high-exposure groups. The kidney evaluation included examination for the presence of $\alpha_{2\mu}$-globulin droplets. Additional end points evaluated in the parental generations included clinical observations, mortality, body weight, and food consumption. Mating and fertility indices were determined for F_0 and F_1 males and females, and gestational, live birth, postnatal survival (4, 7, 14, 21, and 28 days), and lactation indices were determined for the F_1 and F_2 litters.

No effects on reproductive parameters in either generation were reported, although systemic toxicity occurred at all dose levels in F_0 and F_1 adult rats (Tyl and Neeper-Bradley 1989). Hyaline droplet

nephropathy was found in F_0 and F_1 adult males at ≥66 ppm. Manifestations of this male rat-specific renal syndrome included $\alpha_{2\mu}$-globulin accumulation and increased kidney weights at ≥66 ppm, and other characteristic histological changes at 538 ppm. Body weights and weight gains were significantly reduced in F_0 and F_1 adult males and F_1 adult females during the pre-breed exposure periods at 538 ppm. Absolute liver weights were increased in F_0 males by 6, 16, and 38% in the 66, 211, and 538 ppm groups, respectively; the differences were statistically significantly different from control in the 211 and 538 ppm groups. In F_0 females, absolute liver weights were increased by 9 and 31% at 211 and 538 ppm, respectively, but statistical significance was achieved only at 538 ppm. Similar changes were seen in relative liver weights of the F_0 generation, with respective increases of 5, 14, and 52% in the 66, 211, and 538 ppm males and 4, 9, and 31% in the 66, 211, and 538 ppm females; all groups of treated males, and the 211 and 538 ppm female groups, were statistically significantly different from controls. Relative liver weights were also significantly increased in F_1 adult males at ≥211 ppm and in F_1 adult females at 538 ppm. Hepatocellular hypertrophy was observed in the livers of F_0 and F_1 males and females at 538 ppm; no hepatic histological changes were induced at the lower exposure concentrations. Other effects also occurred in the F_0 and F_1 males and females at 538 ppm, indicating that there was a consistent pattern of adult toxicity at the high exposure level, including reduced food consumption and increased incidences of clinical signs (e.g., tremors, unkempt appearance, urine stains, salivation, and nasal and ocular discharges); these effects only sporadically occurred at 211 ppm. Other effects at 538 ppm included reduced gestational and lactational body weight gain, and postnatal toxicity, as evidenced by increased number of stillborn pups, reduced pup body weight, and reduced postnatal survival in F_1 and/or F_2 litters. This study identified: (1) a NOAEL of 66 ppm and LOAEL of 211 ppm for increased (>10% above controls) relative liver weight in adult rats, and (2) a serious LOAEL of 538 ppm for systemic toxicity (central nervous system and other clinical signs) in adult rats and developmental toxicity (increased stillbirths and perinatal mortality) in their offspring (Tyl and Neeper-Bradley 1989). The identification of increased liver weight as a critical effect of 1,4-DCB toxicity is supported by findings of increased liver weight and serum liver enzyme levels and histopathologic liver lesions following repeated oral exposure (Naylor and Stout 1996).

Benchmark dose (BMD) analysis of the male rat serum ALT data (Aiso et al. 2005a) was conducted using all appropriate continuous-variable models in the EPA Benchmark Dose Software (Version 1.3.2) and a benchmark response (BMR) of 1 standard deviation change from the control mean. None of the models provided an adequate fit to the variance, precluding the use of this data set for selecting a point of departure for deriving an MRL. Available continuous-variable models were also fit to the Tyl and Neeper-Bradley (1989) data for changes in liver weight in male rats using a BMR of 1 standard deviation.

The 2-degree polynomial model was the best fitting model, predicting a benchmark concentration (BMC_{1sd}) and $BMCL_{1sd}$ (lower 95% confidence limit on the BMC_{1sd}) of 120 and 92 ppm, respectively. A summary of the predicted BMCs and BMCL for both end points, as well as details of the BMD modeling, are presented in Appendix A.

Using the $BMCL_{1sd}$ of 92 ppm for increased liver weight in male rats and EPA (1994k) inhalation reference concentration (RfC) methodology to determine the MRL, the $BMCL_{1sd}$ of 92 ppm was duration-adjusted for intermittent exposure, as follows:

$$\begin{aligned} BMCL_{1sd\ ADJ} &= (BMCL_{1sd})\ (\text{hours}/24\ \text{hours})\ (\text{days}/7\ \text{days}) \\ &= (92\ \text{ppm})\ (6\ \text{hours}/24\ \text{hours})\ (7\ \text{days}/7\ \text{days}) \\ &= 23\ \text{ppm} \end{aligned}$$

1,4-DCB exhibited the effects outside of the respiratory tract and consequently is treated as a category 3 gas for purposes of calculating the MRL. The human equivalent concentration (HEC) for extrarespiratory effects produced by a category 3 gas is calculated by multiplying the duration-adjusted $BMCL_{1sd}$ ($BMCL_{1sd\ ADJ}$, see below) by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994k). $H_{b/g}$ values were not available for 1,4-DCB in rats and humans. Using a default value of 1 for the ratio of partition coefficients, the $BMCL_{1sd\ HEC}$ becomes 23 ppm:

$$\begin{aligned} BMCL_{1sd\ HEC} &= (BMCL_{1sd\ ADJ})\ \text{x}\ [(H_{b/g})_{RAT} / (H_{b/g})_{HUMAN}], \\ &= 23\ \text{ppm x}\ [1] = 23\ \text{ppm} \end{aligned}$$

The $BMCL_{1sd\ HEC}$ was divided by a total uncertainty factor of 100 to derive the MRL. This uncertainty factor is comprised of component factors of 10 for interspecies extrapolation, and 10 for human variability. Although the rat exposure concentration was adjusted to a HEC, an uncertainty factor of 10 was still applied, because HEC calculation was based on an assumption of equivalent blood-gas partition coefficients, and not on actual data. Dividing the 23 ppm $BMCL_{1sd\ HEC}$ for increased liver weight in male rats by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability) yields an MRL of 0.2 ppm for intermediate-duration inhalation exposure to 1,4-DCB.

Chronic-Duration Exposure.

- An MRL of 0.01 ppm has been derived for chronic-duration (≥365 days) inhalation exposure to 1,4-DCB.

A limited amount of information is available on the long-term toxicity of inhaled 1,4-DCB in humans. Periodic occupational health examinations of workers who were exposed to 1,4-DCB for an average of 4.75 years (range, 8 months to 25 years) showed no changes in standard blood and urine indices (Hollingsworth et al. 1956). The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. Occasional examination of the eyes showed no cataracts or any other lens changes. The odor and irritation properties are considered to be fairly good warning properties that should prevent excessive exposures, although the industrial experience indicates that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor (Hollingsworth et al. 1956). The data from this study are inadequate for chronic MRL derivation due to poor characterization of long-term exposure levels, insufficient investigation of systemic health end points, and reporting and other study deficiencies. Although the available occupational data are insufficient for chronic MRL derivation, the nose and eye irritation findings in humans are consistent with nasal effects observed in chronically exposed animals, as discussed below.

Information on the chronic inhalation toxicity of 1,4-DCB in animals is available from two studies in rats and mice (Aiso et al. 2005b; Japan Bioassay Research Center 1995; Riley et al. 1980a, 1980b). In the Riley et al. (1980a, 1980b) studies, rats of both sexes and female mice were exposed to 75 or 500 ppm of 1,4-DCB for 5 hours/day, 5 days/week for up to 76 weeks (rats) or 57 weeks (mice), followed by 32 weeks (rats) or 18–19 weeks (mice) without exposure. There were no exposure-related histopathological changes in the nasal cavity or other tissues in either species. Liver and kidney weights were increased in rats of both sexes at 500 ppm, but the toxicological significance is questionable due to the negative histopathology findings and the lack of related clinical chemistry effects. Evaluation of the mouse data is limited by reporting insufficiencies in the available summary of the study.

In the other chronic study (Aiso et al. 2005b; Japan Bioassay Research Center 1995), groups of 50 male and female F344/DuCrj rats and 50 male and female Crj:BDF_1 mice were exposed to 1,4-DCB in target concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks. Study end points included clinical signs and mortality, body weight (weekly for the first 13 weeks, and subsequently every 4 weeks), and hematology, blood biochemistry, and urinalysis indices (evaluated at end of study). Selected organ weight measurements (liver, kidneys, heart, lungs, spleen, adrenal, brain, testis, and ovary) and comprehensive gross pathology and histology evaluations were performed on all animals at the end of

the study or at time of unscheduled death. No interim pathology examinations were performed. As summarized below, this study identifies a NOAEL of 20 ppm and a LOAEL of 75 ppm for dose-related eosinophilic changes in the olfactory epithelium in female rats.

For the rats, the actual mean chamber concentrations were 0, 19.8, 74.8, or 298.4 ppm over the duration of the study (Aiso et al. 2005b; Japan Bioassay Research Center 1995). The number of rats surviving to scheduled termination was significantly ($p<0.05$) reduced at 300 ppm in males. Survival in the male rats was noticeably lower than controls beginning at approximately study week 80, and overall survival at 0, 20, 75, and 300 ppm was 66% (33/50), 68% (34/50), 58% (29/50), and 36% (18/50), respectively. There were no exposure-related decreases in survival in the female rats, or effects on growth or food consumption in either sex. Changes in various hematological and blood biochemical indices (mean cell volume, total cholesterol, phospholipids, blood urea nitrogen, creatinine, and calcium in males; total protein, total bilirubin, blood urea nitrogen, and potassium in females) occurred at 300 ppm, but a lack of numerical data and statistical analysis precludes interpretations of significance for these end points. Absolute and relative liver weights in both sexes and kidney weights in males were significantly increased at 300 ppm. Additional findings included histopathological changes in the kidneys and nasal epithelia. The kidney lesions occurred only in male rats at 300 ppm and included significantly increased incidences of mineralization of the renal papilla and in hyperplasia of the urothelium. The nasal lesions mainly included increased incidences of eosinophilic changes (globules) in the olfactory epithelium (moderate or greater severity) in males at 300 ppm and females at ≥75 ppm. Incidences of this lesion at 0, 20, 75, and 300 ppm were 1/50, 2/50, 2/50, and 7/50 in males, and 28/50, 29/50, 39/50, and 47/50 in females. The increases were statistically significant ($p\leq0.05$, Fisher's Exact Test performed by ATSDR) at ≥75 ppm in females and 300 ppm in males, and there was a trend of increasing response with increasing dose in both sexes (Cochran-Armitage test, performed by ATSDR). Other nasal lesions that were significantly increased at 300 ppm were eosinophilic globules in the respiratory epithelium (11/50, 10/50, 14/50, 38/50) and respiratory metaplasia in the nasal gland (5/50, 4/50, 4/50, 33/50) in females at 300 ppm. Kidney lesions were increased only in male rats at 300 ppm and included significantly increased incidences of mineralization of the renal papilla (0/50, 1/50, 0/50, 41/50) and in hyperplasia of the urothelium (7/50, 8/50, 13/50, 32/50).

For the mice, the actual mean chamber concentrations were 0, 19.9, 74.8, or 298.3 ppm over the duration of the study. Survival was significantly reduced in male mice at 300 ppm (due to an increase in liver tumor deaths), but comparable to controls in the females. Terminal body weight was significantly reduced at 300 ppm in males (11.5% less than controls, beginning at study week 80). Changes in various

hematological and blood biochemical indices (total cholesterol, serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactic dehydrogenase [LDH], and alkaline phosphatase [AP] in both sexes; platelet numbers, total protein, albumin, total cholesterol, blood urea nitrogen, and calcium in females) occurred at 300 ppm (Japan Bioassay Research Center 1995), but a lack of reported numerical data and results of statistical analysis precludes interpretation of these end points. Absolute and relative liver and kidney weights in both sexes were significantly increased at 300 ppm. Additional findings included histopathological changes in the nasal cavity, liver, and testes. The nasal lesions included significantly increased incidences of respiratory metaplasia in the nasal gland (moderate severity) in males at 75 ppm (9/49, 12/49, 18/50, 11/49) and olfactory epithelium (slight severity) in males at 75 ppm (23/49, 30/49, 37/50, 22/49) and females at 300 ppm (7/50, 6/50, 2/49, 20/50); the effects in the males were not dose-related (i.e., incidences were increased at 75 ppm but not at 300 ppm). The incidence of centrilobular hepatocellular hypertrophy was significantly increased in male mice at 300 ppm (0/49, 0/49, 0/50, 34/49). Incidences of liver tumors were also increased at 300 ppm; these included hepatocellular carcinoma in males (12/49, 17/49, 16/50, 38/49) and females (2/50, 4/50, 2/49, 41/50), hepatocellular adenoma in females (2/50, 10/50, 6/49, 20/50), hepatoblastoma in males (0/49, 2/49, 0/50, 8/49) and females (0/50, 0/50, 0/49, 6/50), and histiocytic sarcoma in males (0/49, 3/49, 1/50, 6/49). Testicular mineralization was significantly increased in males at ≥75 ppm (27/49, 35/49, 42/50, 41/49) (Japan Bioassay Research Center 1995). The testicular mineralization was not considered to be a toxicologically significant effect (Aiso 2006) because (1) no signs of testicular toxicity were observed in mice exposed for 13 weeks (Aiso et al. 2005a), and (2) it was confined to the testicular capsules and testicular blood vessels and not observed in the testicular parenchyma, indicating that it is a finding commonly observed in aged mice independent of exposure to 1,4-DCB (Aiso 2006).

The results of this study indicate that moderate or severe eosinophilic changes in the nasal olfactory epithelium in female rats is the most sensitive toxic effect in the most sensitive species and sex. The NOAEL and LOAEL for these nasal lesions are 19.8 and 74.8 ppm, respectively. To derive a point of departure for MRL derivation, BMD analysis was conducted using the incidences of the nasal lesions (moderate or greater severity) in the female rats. Data for other end points were not modeled because the effects occurred at higher concentrations (nasal lesions and hepatocellular hypertrophy in mice, kidney lesions in rats) or were not toxicologically significant (testicular mineralization in mice). All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to the female rat nasal lesion incidence data. All models provided adequate fits to the data, and the quantal linear model provided the best fit to the data. Using a BMR level of 10% extra risk above the control incidence, the quantal linear model resulted in a benchmark concentration (BMC_{10}) of 14.08 ppm and lower 95%

confidence limit ($BMCL_{10}$) of 9.51 ppm. A summary of the predicted BMCs and BMCLs, as well as details of the BMD modeling, are presented in Appendix A.

Using the $BMCL_{10}$ value of 9.51 ppm for increased incidences of nasal lesions in female rats and EPA (1994k) inhalation RfC methodology to determine the MRL, the $BMCL_{10}$ was duration-adjusted for intermittent exposure, as follows:

$$\begin{aligned} BMCL_{10\ ADJ} &= (BMCL_{10})\ (\text{hours}/24\ \text{hours})\ (\text{days}/7\ \text{days}) \\ &= (9.51\ \text{ppm})\ (6\ \text{hours}/24\ \text{hours})\ (5\ \text{days}/7\ \text{days}) \\ &= 1.70\ \text{ppm} \end{aligned}$$

For the nasal olfactory epithelium changes in female rats, 1,4-DCB was treated as a category 1 gas with effects in the extrathoracic region for purposes of calculating the HEC. Using EPA (1988, 1994b) reference values, the regional gas deposition ratio was calculated as follows (EPA 1994a):

$$\begin{aligned} RGDR_{ET} &= [(V_E/SA_{ET})_A/(V_E/SA_{ET})_H] \\ &= (0.24\ m^3/\text{day}/15cm^2)/(20\ m^3/\text{day}/200cm^2) \\ &= 0.16 \end{aligned}$$

where: $RGDR_{ET}$ = regional gas deposition ratio in the extrathoracic region
V_E = minute volume in rats $(V_E)_A$ or humans $(V_E)_H$
SA_{ET} = extrathoracic surface area in rats $(SA_{ET})_A$ or humans $(SA_{ET})_H$

The HEC was calculated by multiplying the rat $BMCL_{10\ ADJ}$ by the $RGDR_{ET}$ to yield a $BMCL_{10\ HEC}$ of 0.27 ppm, as follows:

$$\begin{aligned} BMCL_{10\ HEC} &= BMCL_{10\ ADJ} \times RGDR_{ET} \\ &= 1.70\ \text{ppm} \times 0.16 \\ &= 0.27\ \text{ppm} \end{aligned}$$

The $BMCL_{10\ HEC}$ of 0.27 ppm for nasal effects in rats was divided by a total uncertainty factor of 30 to calculate the MRL. This uncertainty factor is comprised of component factors of 3 for interspecies extrapolation and 10 for human variability. A 3-fold uncertainty factor was used instead of a default 10-fold factor to extrapolate from rats to humans, because the dosimetry adjustment (i.e., calculation of the human equivalent exposure for time and concentration [$NOAEL_{HEC}$]) addresses one of the two areas of uncertainty encompassed in an interspecies extrapolation factor. The dosimetric adjustment addresses the pharmacokinetic component of the extrapolation factor, but the pharmaco-dynamic area of uncertainty remains as a partial factor for interspecies uncertainty. Dividing the 0.27 ppm $NOAEL_{10\ HEC}$ by the uncertainty factor of 30 yields an MRL of 0.01 ppm for chronic-duration inhalation exposure to 1,4-DCB.

Oral MRLs

1,2-Dichlorobenzene

Acute-Duration Exposure.

- An MRL of 0.7 mg/kg/day has been derived for acute-duration (≤14 days) oral exposure to 1,2-DCB.

Information on effects of acute oral exposure to sublethal doses of 1,2-DCB consists of findings in three systemic toxicity studies in rats and mice and one developmental toxicity study in rats (NTP 1985; Rimington and Ziegler 1963; Robinson et al. 1991; Ruddick et al. 1983). These studies administered the compound by gavage and collectively identify the liver as the most sensitive target. Severe liver damage, characterized by intense necrosis and fatty changes as well as porphyria, occurred in rats administered 455 mg/kg/day for 15 consecutive days (Rimington and Ziegler 1963). Rats that were exposed to 300 mg/kg/day for 10 consecutive days had hepatic effects that included necrosis and increased serum ALT (Robinson et al. 1991). Hepatocellular degeneration and necrosis occurred in mice that were exposed to 250 or 500 mg/kg/day for 14 consecutive days (NTP 1985). The 15-day rat and 14-day mouse studies are limited by small numbers of animals (3–5 per dose) and lack of a NOAEL due a single dose level (Rimington and Ziegler 1963) or lack of histopathology evaluations at doses lower than the LOAEL (NTP 1985). The 10-day study (Robinson et al. 1991) is the most appropriate basis for MRL derivation because it is well designed, included four dose levels, and provides dose-response data for several hepatic end points.

In the Robinson et al. (1991) study, groups of 10 male and 10 female Sprague-Dawley rats were treated with 1,2-DCB in corn oil by gavage at doses of 0, 37.5, 75, 150, or 300 mg/kg/day for 10 consecutive days. The doses were selected on the basis of a reported rat oral LD_{50} of 500 mg/kg. End points evaluated during the study included clinical signs, body weight, and food and water consumption. Evaluations at the end of the exposure period included hematology (five indices), serum chemistry (nine indices including aspartate AST, ALT, LDH, cholesterol, blood urea nitrogen, and creatinine), and selected organ weights (brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart, and testes or ovaries). Histological examinations were performed on various tissues including liver, kidneys, urinary bladder, heart, skin, muscle, bone, respiratory tract (nasal cavity with turbinates, lungs), nervous system

(brain, sciatic nerve), immunological (spleen, thymus, lymph nodes), gastrointestinal (duodenum, ileum, jejunum, salivary gland, colon, cecum, rectum), endocrine (adrenal glands, pancreas), and reproductive (testes, seminal vesicles, prostate, ovaries) in the high-dose and control groups. Target organs identified in the high-dose group were also histologically evaluated at the lower dose levels.

No clinical signs or effects on survival were observed (Robinson et al. 1991). Body weight gain was significantly reduced in the male rats at 300 mg/kg/day (final body weights were 10.9% lower than controls), but not in females, and there were no exposure-related changes in food consumption in either sex. Statistically significant changes in organ weights predominantly occurred at 300 mg/kg/day, including significantly decreased absolute spleen weight in both sexes and decreased absolute heart, kidney, thymus, and testes weights in males. Liver weight (absolute and relative) was significantly increased in females at ≥150 mg/kg/day and males at 300 mg/kg/day; compared to controls in the low- to high-dose females, absolute liver weights were 1.8, 9.0, 20.5, and 29.0% increased and relative liver weights were 6.8, 7.6, 21.7, and 34.5% increased. Clinical chemistry findings included significantly increased serum ALT in both sexes at 300 mg/kg/day and serum phosphorus in females at ≥150 mg/kg/day. Serum cholesterol was significantly increased in females at ≥37.5 mg/kg/day, but the toxicological significance is unclear because the values were similar at all dose levels and showed no dose-response. Histopathological findings were limited to the liver and included necrosis that was slight in severity and significantly ($p=0.04$) increased in males at 300 mg/kg/day (4/10 compared to 0/10 in controls); incidences in the other dose groups were not reported, although the study authors indicated that target organs in the high-dose groups were histologically evaluated at the lower dose levels. Incidences of other hepatic lesions were not significantly increased, but included inflammation (characterized by lymphocyte and macrophage infiltrates) and degeneration of hepatocytes (characterized by varying degrees of fibrillar or vacuolated cytoplasm and swelling with intact cell membranes). This study identified a NOAEL of 75 mg/kg/day and a LOAEL of 150 mg/kg/day for increased liver weight (>10%) in female rats, as well as a LOAEL of 300 mg/kg/day for liver necrosis in male rats.

To derive a point of departure for MRL derivation, BMD dose analysis was conducted using the rat absolute liver weight data. The liver lesion data were not subjected to BMD analysis because incidences of liver necrosis were only reported for control and high-dose rats. Serum liver enzyme (ALT, AST, LDH) data were not subjected to BMD analysis because a statistically significant increase was noted only for serum ALT in the high-dose group of male rats and the magnitude of the increase (50% higher than the control serum ALT level) is not considered to be adverse. All continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the absolute liver weight data from male and female

rats. One standard deviation increase from the control mean value was selected as the BMR in the absence of a biological rationale for using an alternative BMR. A summary of the predicted BMDs and BMDLs, as well as details of the BMD modeling, are presented in Appendix A. The linear model was determined to the best-fitting model for the liver weight data in male rats (provided a BMD_{1sd} of 249.04 mg/kg/day and a $BMDL_{1sd}$ of 158.55 mg/kg/day) and female rats (provided a BMD_{1sd} of 84.67 mg/kg/day and a $BMDL_{1sd}$ of 67.73 mg/kg/day). Among the best-fitting model results, the lowest $BMDL_{1sd}$ of 67.73 mg/kg/day was selected as the point of departure for deriving the MRL. The $BMDL_{1sd}$ of 67.73 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive an MRL of 0.7 mg/kg/day for acute-duration oral exposure to 1,2-DCB.

Intermediate-Duration Exposure.

- An MRL of 0.6 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,2-DCB.

Information on effects of intermediate-duration oral exposure to 1,2-DCB is available from three intermediate studies in rats and mice identifying the liver as the most sensitive target of toxicity (Hollingsworth et al. 1958; NTP 1985; Robinson et al. 1991). Incidences of degenerative liver lesions were significantly increased in rats exposed to 250–500 mg/kg/day for ≥13 weeks (Hollingsworth et al. 1958; NTP 1985; Robinson et al. 1991) and mice exposed to 250 mg/kg/day for 13 weeks (NTP 1985). Necrotic lesions occurred in several rats at 125 mg/kg/day (1/10 males, 3/10 females), but the increase was not statistically significant (NTP 1985). Other hepatic findings in rats exposed to lower doses (125–188 mg/kg/day for ≥13 weeks) included increases in relative liver weight and serum levels of ALT, cholesterol, serum protein, and decreases in serum triglycerides. Increased serum ALT is an inconsistent finding because it was induced in rats exposed to ≥100 mg/kg/day for 90 days (Robinson et al. 1991), but not in rats exposed to ≥125 mg/kg/day for 13 weeks (NTP 1985). Additionally, the increase in serum ALT was not dose-related and serum levels of other liver-associated enzymes were not increased in either the Robinson et al. (1991) study (AST, LDH, and AP) or the NTP (1985) study (AP and GGTP). The lowest LOAEL is 125 mg/kg/day, which is a minimal LOAEL for increased liver weight in rats in the NTP (1985) study.

In the NTP (1985) study, groups of 10 male and 10 female F344 rats and 10 male and 10 female $B6C3F_1$ mice were administered 1,2-DCB in doses of 0, 30, 60, 125, 250, or 500 mg/kg/day for

5 days/week for 13 weeks. Histology examinations of the liver were limited to the control and three highest dose groups. Degenerative lesions were significantly ($p \leq 0.05$) increased in both species at ≥250 mg/kg/day. Changes in the rats included necrosis of individual hepatocytes at ≥250 mg/kg/day and centrilobular degeneration at 500 mg/kg/day; total incidences of these lesions at 0, 125, 250, and 500 mg/kg/day were 0/10, 1/10, 4/9, and 8/10 in males, and 0/10, 3/10, 5/10, and 7/8 in females. Relative liver weights were significantly increased at 125, 250, and 500 mg/kg/day in the males (8, 17, and 45% higher than controls) and females (8, 15, and 30%); increased relative liver weights were not seen at lower doses in either sex. There were no increases in serum levels of liver enzymes [ALT, AP, or GGPT] at any dose in either sex. Serum cholesterol was significantly increased in males at ≥30 mg/kg/day (50.0, 17.6, 26.5, 70.6, and 109% higher than controls in the low to high dose groups; not significant at 60 mg/kg/day) and females at ≥125 mg/kg/day (12.2, 12.2, 32.6, 26.5, and 51.0%). Although increases in serum cholesterol were observed at doses as low as 30 mg/kg/day, the toxicological significance is unclear because there was no clear dose-response unless the increase at 30 mg/kg/day is considered to be outlying. Urinary concentrations of uroporphyrin and coproporphyrin were 3–5 times higher than controls in the 500 mg/kg/day males and females, but this increase was not considered indicative of porphyria because total porphyrin concentration in the liver was not altered at any dose level and no pigmentation indicative of porphyria was observed by ultraviolet light at necropsy. The 60 and 125 mg/kg/day doses are the NOAEL and LOAEL, respectively, for hepatic effects in rats based on the increases in liver weight in both sexes.

In the mice, no compound-related histopathological changes were observed in either sex at 0 and 125 mg/kg/day or in females at 250 mg/kg/day. Lesions that were significantly increased included necrosis of individual hepatocytes, hepatocellular degeneration and/or pigment deposition in 4/10 males at 250 mg/kg/day, and centrilobular necrosis, necrosis of individual hepatocytes, and/or hepatocellular degeneration in 9/10 males and 9/10 females at 500 mg/kg/day. Relative liver weights were significantly increased at 500 mg/kg/day in both sexes, but there were no exposure-related changes in serum levels of ALT, AP, or GGPT in either sex at any dose (no other clinical chemistry indices were examined in the mice). Based on the liver lesion data, the NOAEL and LOAEL in mice are 125 and 250 mg/kg/day, respectively.

To derive a point of departure for MRL derivation, BMD analysis was conducted using liver lesion and liver weight data from the NTP (1985) study. Dichotomous models available in the EPA Benchmark Dose Software (Version 1.3.2) were fit to data for incidences of liver lesions (single cell necrosis, centrilobular necrosis, and/or hepatocellular degeneration) in male and female rats (combined) and male

mice. Because there were no apparent differences in sensitivity to 1,2-DCB among the male and female rats, the liver lesion data were combined to increase the statistical power for BMD analysis. For each data set, BMDs and their lower 95% confidence limits (BMDLs) were calculated using a BMR of 10% extra risk. All available models provided adequate fit to liver lesion data for male and female rats combined. The best-fitting model was the quantal quadratic model, which provided a BMD_{10} of 108.71 mg/kg/day and a $BMDL_{10}$ of 92.08 mg/kg/day. The log-probit model was determined to be the best-fitting model for the male mouse incidence data and provided a BMD_{10} of 176.05 mg/kg/day and $BMDL_{10}$ of 114.58 mg/kg/day. Continuous variable models in the EPA Benchmark Dose Software were fit to the relative liver weight data for male and female rats using a BMR of 1 standard deviation from the control mean. Adequate fits were not obtained for the male rat liver weight data, but the linear model was the best-fitting model for the female data, resulting in a BMD_{1sd} of 108.15 mg/kg/day and a $BMDL_{1sd}$ of 89.27 mg/kg/day. A summary of the predicted BMDs and BMDLs for both end points, as well as details of the BMD modeling, are presented in Appendix A.

The $BMDL_{1sd}$ of 89.27 mg/kg/day from the best-fitting modeling results of the female rat relative liver weight data is lower than the $BMDL_{10}$ of 92.08 mg/kg/day from the best-fitting modeling results of liver lesion incidences in the male and female rats combined and the $BMDL_{10}$ of 114.58 mg/kg/day from the best-fitting model results of liver lesion incidences in the male mice. Therefore, the $BMDL_{1sd}$ of 89.27 mg/kg/day for increased relative liver weight in the female rats was selected as the point of departure for the MRL. The $BMDL_{1sd}$ of 89.27 mg/kg/day was adjusted for intermittent experimental exposure (5 days/7 days) to give a duration-adjusted $BMDL_{1sd}$ of 63.76 mg/kg/day, and divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive an intermediate-duration oral MRL of 0.6 mg/kg/day for 1,2-DCB.

Chronic-Duration Exposure.

- An MRL of 0.3 mg/kg/day has been derived for chronic-duration (≥365 days) oral exposure to 1,2-DCB.

One chronic oral toxicity study of 1,2-DCB is available. In this study groups of F344/N rats (50/sex/group) and $B6C3F_1$ mice (50/sex/group) were administered 1,2-DCB in corn oil by gavage in doses of 0, 60, or 120 mg/kg/day for 5 days/week for 103 weeks (NTP 1985). Evaluations included clinical signs, body weight, and necropsy and histology on all animals. Organ weight and clinical chemistry indices were not assessed. The only exposure-related effect in either species was a

significantly increased incidence of renal tubular regeneration in the male mice. This lesion showed a dose-related trend, and was statistically significantly elevated in high-dose animals, but not in low-dose animals. The NOAEL for the lesion was therefore 60 mg/kg/day, and the LOAEL was 120 mg/kg/day.

To derive a point of departure for MRL derivation, BMD analysis was conducted using the kidney lesion incidence data. All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to the male mouse incidence data for renal tubule regeneration. A 10% extra risk above the control incidence was selected as the BMR in the absence of a biological rationale for using an alternative BMR. A summary of the predicted BMDs and BMDLs, as well as details of the BMD modeling, are presented in Appendix A. The logistic model was the best-fitting model, resulting in a BMD_{10} of 62.96 mg/kg/day and a $BMDL_{10}$ of 43.04 mg/kg/day. The $BMDL_{10}$ 43.04 mg/kg/day was adjusted for intermittent experimental exposure (5 days/7 days) to give a duration-adjusted $BMDL_{10}$ of 30.74 mg/kg/day, and divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive a chronic-duration oral MRL of 0.3 mg/kg/day for 1,2-DCB.

1,3-Dichlorobenzene

Acute-Duration Exposure.

- An MRL of 0.4 mg/kg/day has been derived for acute-duration (≤14 days) oral exposure to 1,3-DCB.

The acute oral database for 1,3-DCB consists of one short-term toxicity study in which groups of 10 male and 10 female Sprague Dawley rats were administered gavage doses of 0, 37, 147, 368, or 735 mg/kg/day in corn oil for 10 consecutive days (McCauley et al. 1995). End points evaluated during the study included clinical signs, survival, body weight, and food and water consumption. At the end of the study, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), and selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads). Gross pathology was evaluated in all animals, and comprehensive histological examinations were performed in the high dose and control groups; histology in the lower dose groups was limited to the liver. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

No compound-related deaths or overt clinical signs were observed (McCauley et al. 1995). Body weight was significantly reduced in both sexes at 735 mg/kg/day (20 and 13% lower than controls in males and females, respectively). Food consumption was significantly decreased at 735 mg/kg/day in males (12%, normalized by body weight), and water consumption was significantly increased (8–13%) in females at ≥735 mg/kg/day. The hematological evaluation showed 8% decreased MCV in females at 735 mg/kg/day. The clinical chemistry analyses showed statistically significant changes in several indices, but serum cholesterol was the only end point that had values that exceeded the reference range. Serum cholesterol was significantly increased in females at 368 and 735 mg/kg/day (94 and 63% higher than controls, respectively), as well as in males at 368 and 735 mg/kg/day (79 and 84% higher than controls, respectively). Relative liver weight was significantly increased in males at ≥147 mg/kg/day and females at ≥368 mg/kg/day; increases in the males were 9.1, 31.3, 50.63, and 32.5% higher than controls in the low- to high-dose groups. Other significant changes in relative organ weight included decreased spleen weight in females at ≥368 mg/kg/day and males at 735 mg/kg/day, decreased thymus weight in both sexes at 735 mg/kg/day, and decreased testes weight in males at 735 mg/kg/day. Absolute organ weights were not reported. Histological changes primarily occurred in the liver, particularly centrilobular hepatocellular degeneration at ≥368 mg/kg/day. This lesion was characterized by varying degrees of cytoplasmic vacuolization and swelling with intact membranes, and occurred in the 368 and 735 mg/kg/day groups in 2/10 and 9/10 males, respectively, and 6/10 and 10/10 females, respectively; incidences in the other groups were not reported but are presumed to be 0/10. Other hepatic alterations included hepatocellular necrosis that was sporadically noted in the 147, 368, and 735 mg/kg/day groups. This change was usually minimal to mild, and was reported to increase in incidence and severity in the males in a dose-related manner; however, incidences were not reported. The only other reported histological change was atrophy of the thymus, characterized by loss of normal differentiation between medulla and cortex. The thymic atrophy was observed in 2/10 males (both marked in severity) and 2/9 females (both mild in severity) at 735 mg/kg/day; this change was not observed in controls, and the other dosed groups were not examined. The 147 mg/kg/day dose is the LOAEL (minimal) for liver effects based on the >10% increase in relative liver weight in male rats. The NOAEL for increased liver weight is 37 mg/kg/day.

To derive a point of departure for MRL derivation, BMD analysis was conducted using liver effects data from the McCauley et al. (1995) study. The liver effects data modeled included incidences of hepatocellular degeneration, absolute liver weights and mean serum cholesterol levels. All dichotomous variable models available in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the incidence data for hepatocellular degeneration in male and female rats using a BMR of 10% extra risk. All

continuous variable models in the BMD software were fit to the mean absolute liver weight data and mean serum cholesterol level data in male and female rats using a BMR of 1 standard deviation increase above the control mean. A summary of the predicted BMDs and BMDLs for all end points, as well as details of the BMD modeling, are presented in Appendix A. The best-fitting models resulted in a $BMDL_{10}$ of 207.86 mg/kg/day for hepatocellular degeneration in male rats (log-probit model), a $BMDL_{10}$ of 159.37 mg/kg/day for hepatocellular degeneration in female rats (log-probit model), and a $BMDL_{1sd}$ of 36.32 mg/kg/day for absolute liver weight changes in female rats (2-degree polynomial model). The lowest $BMDL_{1sd}$ of 36.32 mg/kg/day was selected as the most conservative point of departure for deriving an MRL. The $BMDL_{1sd}$ of 36.32 mg/kg/day was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive an acute-duration oral MRL of 0.4 mg/kg/day for 1,3-DCB.

Intermediate-Duration Exposure.

- An MRL of 0.02 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,3-DCB.

The database for intermediate-duration oral exposure to 1,3-DCB consists of one intermediate toxicity study in which groups of 10 male and 10 female Sprague Dawley rats were administered gavage doses of 0, 9, 37, 147, or 588 mg/kg/day in corn oil for 90 consecutive days (McCauley et al. 1995). End points evaluated during the study included clinical signs and mortality, body weight, and food and water consumption. At end of the exposure period, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads), and gross pathology was assessed. Histological examinations were performed on all tissues that were examined grossly in all high-dose rats and in one-half of control rats, as well as in the liver, thyroid, and pituitary glands from all animals in the 9, 37, and 147 mg/kg/day dose groups. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

No compound-related deaths or overt clinical signs were observed (McCauley et al. 1995). Body weight was reduced in both sexes at 588 mg/kg/day (24 and 10% lower than controls in males and females, respectively). The decreased weight gain was progressive throughout the exposure period and occurred

despite increased food and water consumption in the same groups. Other effects included increased relative kidney weight in males at ≥147 mg/kg/day and females at 588 mg/kg/day, but there were no renal histopathological changes in any of the exposed animals. Hematological alterations consisted of significant increases in leukocyte levels in males at 147 mg/kg/day and females at 588 mg/kg/day, and in erythrocyte levels in males at 588 mg/kg/day. As discussed below, histopathology and serum chemistry findings indicated that the thyroid, pituitary, and liver were the most sensitive targets of toxicity.

Thyroid effects included significantly ($p \leq 0.05$) increased incidences of reduced colloidal density in follicles that exceeded normal variability in male rats at ≥9 mg/kg/day and female rats at ≥37 mg/kg/day (control to high dose group incidences of 2/10, 8/10, 10/10, 8/9, and 8/8 in males, and 1/10, 5/10, 8/10, 8/10, and 8/9 in females) (McCauley et al. 1995). Depletion of colloid density in the thyroid was characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar. The severity of the colloid density depletion generally ranged from mild to moderate, increased with dose level, and was greater in males than females. Incidences of male rats with thyroid colloidal density depletion of moderate or marked severity were significantly increased at ≥147 mg/kg/day (0/10, 0/10, 2/10, 5/9, and 6/8).

Pituitary effects included significantly ($p \leq 0.05$) increased incidences of cytoplasmic vacuolization in the pars distalis in male rats at ≥147 mg/kg/day (2/10, 6/10, 6/10, 10/10, and 7/7). The vacuoles were variably sized, irregularly shaped, and often poorly defined, and the severity of the lesions (i.e., number of cells containing vacuoles) ranged from minimal to mild and generally increased with increasing dose level. Incidences of male rats with pituitary cytoplasmic vacuolization of moderate or marked severity were significantly increased at 588 mg/kg/day (1/10, 0/10, 2/10, 3/9, and 7/7). The pituitary lesion was reported to be similar to "castration cells" found in gonadectomized rats and considered to be an indicator of gonadal deficiency. No compound-related pituitary lesions were observed in female rats. Serum cholesterol was significantly increased in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day in a dose-related manner, and serum calcium was significantly increased in both sexes at ≥37 mg/kg/day. The investigators suggested that these serum chemistry changes might reflect a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs.

Hepatic effects occurred in both sexes at 147 and 588 mg/kg/day, including significantly increased relative liver weight and incidences of liver lesions (McCauley et al. 1995). Absolute organ weights were not reported. Liver lesions were characterized by inflammation, hepatocellular alterations (eosinophilic

homogeneous inclusions), and hepatocellular necrosis. Liver lesions that were significantly ($p \leq 0.05$) increased included hepatocellular cytoplasmic alterations of minimal to mild severity in males at ≥147 mg/kg/day (1/10, 2/10, 1/10, 6/10, and 7/9) and females at 588 mg/kg/day (0/10, 2/10, 0/10, 1/10, and 7/9), and necrotic hepatocyte foci of minimal severity at 588 mg/kg/day in both males (1/10, 2/10, 1/10, 2/10, and 5/9) and females (0/10, 0/10, 0/10, 3/10, and 5/9). Other statistically significant liver-associated effects included significantly increased serum AST levels (90–100% higher than controls) in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day. Serum cholesterol levels were significantly increased in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day, but might be pituitary-related, as indicated above. Serum LDH levels were reduced in males at ≥9 mg/kg/day and BUN levels were reduced in both sexes at 588 mg/kg/day, but the biological significance of decreases in these indices is unclear.

To derive a point of departure for MRL derivation, BMD analysis was conducted using data for thyroid and pituitary lesion incidences and serum AST and cholesterol levels. Continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to serum AST levels in the male rats and the serum cholesterol levels in the male and female rats using a one standard deviation change from the control mean as the BMR. Dichotomous variable models in the BMD software were fit to the incidence data for thyroid lesions (reduced follicular colloidal density) and pituitary lesions (cytoplasmic vacuolation in the pars distalis) in the male rats. A summary of the predicted BMDs and BMDLs for all of the end points, as well as details of the BMD modeling, are presented in Appendix A. None of the models provided an adequate fit for the serum AST, serum cholesterol, or thyroid lesion data. For the pituitary lesion incidence data, all of the models provided adequate fit. The probit model provided the best fit, but nearly identical fits were provided by three other models (gamma, quantal-linear, and Weibull). Because the BMD_{10} of 4.08 mg/kg/day and associated $BMDL_{10}$ of 2.10 mg/kg/day from the gamma, quantal-linear, and Weibull models are lower than those from the probit model (BMD_{10} = 7.79 mg/kg/day; $BMDL_{10}$ = 4.46 mg/kg/day), a conservative health protective approach was taken and the lower $BMDL_{10}$ of 2.10 mg/kg/day was selected as the point of departure for deriving the MRL. The $BMDL_{10}$ of 2.1 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive an MRL of 0.02 mg/kg/day for intermediate-duration oral exposure to 1,3-DCB.

Chronic-Duration Exposure.

No MRL was derived for chronic-duration oral exposure to 1,3-DCB due to a lack of chronic oral studies.

1,4-Dichlorobenzene

Acute-Duration Exposure. No acute-duration oral MRL was derived for 1,4-DCB due to insufficient data. Information on effects of non-lethal acute-duration oral exposures to 1,4-DCB is essentially limited to hepatic and renal changes of unclear toxicological significance observed in studies designed to elucidate mechanisms of liver and kidney toxicity in rats and mice. Acute liver damage, as assessed by histopathology and serum enzyme/biochemical indicators following gavage exposure, was not induced by high levels of 1,4-DCB in rat given single doses of ≤2790 mg/kg (Allis et al. 1992), rats and mice given single doses of ≤1,200 mg/kg/day (Eldridge et al. 1992), or rats and mice administered ≤300 and ≤600 mg/kg/day, respectively, 5 days/week for 1 week (Lake et al. 1997). Porphyria, manifested as increased porphyrin levels in liver and urine and suggestive of hepatic damage, was reported in rats that were orally exposed to 770 mg/kg/day for 5 days (Rimington and Ziegler 1963). Although there was no clear evidence of liver injury in acute studies, similar dose levels of 1,4-DCB are toxic following intermediate- and chronic-duration exposures.

Increased hepatocelluar proliferation, as measured by increased incorporation of bromodeoxyridine (BrdU) or [3H] thymidine into DNA-synthesizing liver cells, has been demonstrated in rats and mice at doses ≥150 mg/kg/day in a number of single dose and short-term oral studies that found no histological or other indications of overt liver damage (Eldridge et al. 1990, 1992; Hasmall et al. 1997; Lake et al. 1997; Sherman et al. 1998; Umemura et al. 1992, 1996). The induction of liver cell proliferation in the absence of manifest hepatoxicity suggests that the proliferation is a response to mitogenic stimulation rather than compensatory regeneration to cytotoxicity. Cellular proliferation and other changes have also been demonstrated in the kidney tubular epithelia of male rats, but not in female rats or mice of either sex, following short-term oral exposures to doses ≥150 mg/kg/day (Eldridge et al. 1992; Lake et al. 1997; Sherman et al. 1998; Umemura et al. 1992). The renal effects are consistent with the induction of $\alpha_{2\mu}$-globulin nephropathy in male rats by similar doses of 1,4-DCB in other acute oral studies (Charbonneau et al. 1989b; Dietrich and Swenberg 1991; Saito et al. 1996), but are not relevant to humans. Induction of hepatic microsomal xenobiotic metabolizing enzymes appears to be the most sensitive effect of acute/short-term exposure to 1,4-DCB (Elovaara 1998). For example, oral exposure to doses as low as 20 mg/kg/day for 14 days increased the activities of glucuronyl transferase, benzpyrene

hydroxylase, and enzymes involved in the detoxification of O-ethyl-O-nitrophenyl phenylphosphorothionate (EPN) in rats (Carlson and Tardiff 1976). Induction of hepatic microsomal enzymes is not necessarily adverse, but does indicate that the liver is sensitive to relatively low doses of 1,4-DCB.

The toxicological significance of the hepatic microsomal enzyme changes is unclear and the information on other liver effects is insufficient to identify a reliable NOAEL or LOAEL for acute/short-term oral exposure to 1,4-DCB. The lack of adequate data on the threshold of adverse effects precludes derivation of an MRL for acute duration oral exposure.

Intermediate-Duration Exposure.

- An MRL of 0.07 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,4-DCB.

Information on the systemic toxicity of intermediate-duration oral exposure to 1,4-DCB is available from a number of studies conducted in rodents, mainly rats and mice, as well as one study in dogs. Liver and kidney effects are the most consistently observed, best characterized, and most sensitive findings in these studies. The lowest observed adverse effect level is for liver toxicity in dogs, although reproductive and developmental studies in rats indicate that offspring are particularly sensitive to 1,4-DCB toxicity during the postnatal preweaning period.

Hepatic effects induced by intermediate-duration oral exposures to 1,4-DCB ranged from increased liver weight and hepatocyte enlargement to hepatocellular degeneration, lesions, necrosis, and tumors in rats, mice, rabbits, and dogs. Increases in serum levels of enzymes and alterations in other end points (e.g., serum cholesterol and triglycerides) indicative of hepatocellular damage or liver dysfunction have also been induced. Increased liver weight is the most sensitive hepatic end point in intermediate-duration studies in rats, observed at doses as low as 150 mg/kg/day for 4–13 weeks and 188 mg/kg/day for 192 days (Hollingsworth et al. 1956; Lake et al. 1997; Umemura et al. 1998). There was no indication of early liver damage in rats exposed to 150 mg/kg/day for 4 weeks using an immunohistochemical marker of centrilobular hepatocyte injury (Umemura et al. 1998), and increases in liver porphyrins in rats exposed to 50–200 mg/kg/day for 120 days were not considered to be toxicologically significant (Carlson 1977). Hepatocellular hypertrophy and decreased serum triglycerides occurred in rats exposed to ≥300 mg/kg/day for 13 weeks (Lake et al. 1997; NTP 1987). Higher dose levels of 1,4-DCB induced degenerative liver lesions in rats exposed to 376 mg/kg/day for 192 days (slight cirrhosis and focal

necrosis) (Hollingsworth et al. 1956) or 1,200 mg/kg/day for 13 weeks (hepatocyte degeneration and necrosis) (NTP 1987). In mice, hepatocellular degeneration was induced at doses ≥600 mg/kg/day for 13 weeks (NTP 1987), and rabbits had cloudy swelling and minimal focal necrosis in the liver after exposure to 500 mg/kg/day for 367 days (Hollingsworth et al. 1956). Dogs are more sensitive to hepatic effects of intermediate-duration 1,4-DCB exposure than the other species because serum enzyme levels were increased following exposure to doses as low as 50 mg/kg/day for 6 months (Naylor and Stout 1996).

Renal changes, including hyaline droplet accumulation, increased kidney weights, and tubular lesions, are characteristically observed effects of subchronic and chronic oral exposure to 1,4-DCB in male rats at doses ≥75 mg/kg/day (Bomhard et al. 1988; Lake et al. 1997; NTP 1987). These findings are not considered for MRL derivation because there is a scientific consensus that they are related to the $\alpha_{2\mu}$-globulin nephropathy syndrome, which is specific to male rats and not relevant to humans. Subchronic studies in female rats found increased kidney weight, but no indications of nephrotoxic action (i.e., no histopathology or effects on urinary indices of renal function), following exposure to ≥188 mg/kg/day for 192 days or 600 mg/kg/day for 13 weeks (Bomhard et al. 1988; Hollingsworth et al. 1956).

Developmental toxicity studies provide no indications that 1,4-DCB is teratogenic in rats at oral doses as high as 1,000 mg/kg/day during gestation, although fetotoxicity occurred at maternally toxic levels ≥500 mg/kg/day (Giavini et al. 1986; Ruddick et al. 1983). Decreased maternal weight gain and increased incidences of extra ribs, a skeletal variation attributable to the maternal toxicity, occurred in rats at gestational dose levels ≥500 mg/kg/day, but not at 250 mg/kg/day (Giavini et al. 1986). In a two-generation study, reproductive and developmental toxicity were evaluated in male and female rats that were orally exposed to 30, 90, or 270 mg/kg/day of 1,4-DCB (Bornatowicz et al. 1994). No effects on mating and fertility indices were observed at any level, although toxicity occurred in the offspring at doses ≥90 mg/kg/day. Effects at ≥90 mg/kg/day included reduced birth weight in F_1 pups and increased total number of deaths from birth to postnatal day 4 in F_1 and F_2 pups, clinical manifestations of dry and scaly skin (until approximately postnatal day 7) and tail constriction with occasional partial tail loss (during postnatal days 4–21) in F_1 and F_2 pups, reduced neurobehavioral performance (draw-up reflex evaluated at weaning) in F_2 pups, and increased relative liver weight in adult F_1 males. No exposure-related changes were found at 30 mg/kg/day, indicating that this is the NOAEL for reproductive and developmental toxicity in rats.

As discussed above, liver, kidney, and perinatal developmental toxicity are main effects of concern for intermediate-duration oral exposure to 1,4-DCB in animals. The dog is the most sensitive tested species, as liver effects were induced by exposure to doses as low as 50 mg/kg/day for 6 months (Naylor and Stout 1996), which are below subchronic LOAELs of approximately 150–200 mg/kg/day for liver and kidney effects in rats and mice. The two-generation study in rats demonstrates that oral exposure to 1,4-DCB can cause perinatal developmental toxicity, including reduced birth weight and neonatal survival in F_1 and F_2 pups, at doses ≥90 mg/kg/day (Bornatowicz et al. 1994). Although this finding indicates that perinatal developmental toxicity is an additional sensitive end point for 1,4-DCB exposure, the lower 50 mg/kg/day LOAEL for liver effects in dogs (Naylor and Stout 1996) is a more appropriate basis for MRL derivation.

In the dog study, groups of five male and five female beagles were orally administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day on 5 days/week for 1 year (Naylor and Stout 1996). Complete details on the experimental design and results of the study are provided in the section on the chronic oral MRL for 1,4-DCB. As summarized below, 6-month interim liver enzyme findings are consistent with liver enzyme, liver weight, and histopathological changes observed at 1 year. Hepatic end points evaluated at 6 months were limited to clinical chemistry indices, including serum ALT, AST, GGTP, and AP, whereas the 1-year end-of-study evaluations included liver weight and histology in addition to clinical chemistry. Effects on serum enzymes included statistically significantly increased AP in males at 50 mg/kg/day after 6 and 12 months, females at 50 mg/kg/day after 6 and 12 months, and females at 75 mg/kg/day after 6 and 12 months. Serum AP levels were not statistically significantly increased in the 75 mg/kg/day males at months 6 or 12, but only three animals were evaluated in this dose group. As detailed in the chronic MRL summary, the increases in serum AP were similar in magnitude after 6 and 12 months, ranging from 330 to 761% higher than control values. Other clinical chemistry findings included significantly increased serum ALT (75 mg/kg/day females at month 12) and GGTP (75 mg/kg/day females at months 6 and 12), and significantly decreased albumin (50 and 75 mg/kg/day in males at months 6 and 12, and 75 mg/kg/day in females at month 6). Absolute and relative liver weights were significantly increased in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatic lesions included hepatocellular hypertrophy (diffuse or multifocal in all males and females at 50 and 75 mg/kg/day, and one female at 10 mg/kg/day), hepatocellular pigment deposition (two males and one female each at 50 and 75 mg/kg/day), bile duct/ductule hyperplasia (one male and one female at 75 mg/kg/day), and hepatic portal inflammation (periportal accumulation of neutrophils in one male at 50 mg/kg/day and two males at 75 mg/kg/day). The 50 mg/kg/day dose is a intermediate-duration LOAEL based on the increases in serum AP at 6 months. This serum enzyme change is a sufficient indication of intermediate-duration hepatotoxicity because the increases were

similar in magnitude to those observed after 1 year and associated with increased liver weight and liver lesions; the latter effects likely developed earlier in the study but could not be detected due to the lack of organ weight and histology examinations before 1 year.

To derive a point of departure for MRL derivation, BMD analysis was conducted using the Naylor and Stout (1996) data for changes in serum AP levels in female dogs. Mean serum AP levels in the female dogs exhibited a dose-response relationship and were significantly increased in the 50 and 75 mg/kg/day groups. Although significantly increased mean serum AP levels were noted in the 50 mg/kg/day male dogs, the increase was not significant in the 75 mg/kg/day males; only three males in this dose group were available for the assessment of serum AP levels. Therefore, the male serum AP data were not modeled. Continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to serum AP data in the female dogs using a one standard deviation change from the control mean as the BMR. A summary of the predicted BMDs and BMDLs, as well as details of the BMD modeling, are presented in Appendix A. The best fit was provided by the polynomial model, which resulted in a BMD_{1sd} of 12.48 mg/kg/day and a $BMDL_{1sd}$ of 9.97 mg/kg/day. The $BMDL_{1sd}$ of 9.97 mg/kg/day was adjusted for intermittent experimental exposure (5 days/7 days) to give a duration-adjusted $BMDL_{1sd}$ of 7 mg/kg/day, and divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive an intermediate-duration oral MRL of 0.07 mg/kg/day for 1,4-DCB.

Chronic-Duration Exposure.

- An MRL of 0.07 mg/kg/day has been derived for chronic-duration (365 days or more) oral exposure to 1,4-DCB.

Information on the chronic oral effects of 1,4-DCB is available from one study each in rats, mice, rabbits, and dogs. Observed effects included nephropathy in rats (including tubular degeneration and atrophy in females) exposed to ≥150 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), hepatocellular degeneration and nephropathy in mice exposed to ≥300 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), and cloudy swelling and minimal focal necrosis in rabbits exposed to 500 mg/kg/day in 263 doses in 367 days (Hollingsworth et al. 1956). The lowest chronic LOAEL in these studies was 150 mg/kg/day for kidney effects in female rats (NTP 1987). Liver and kidney effects were induced in dogs at doses below the LOAELs in the other species. As summarized below, doses as low as 50 mg/kg/day for 1 year were hepatotoxic in dogs (Naylor and Stout 1996).

In the dog study, groups of five male and five female beagles were orally administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day for 1 year (Naylor and Stout 1996). Based on the summarized design of a 4-week dose range-finding study, it is presumed that dosing was 5 days/week. The 75 mg/kg/day dose is a time-weighted average level reflecting dose decreases at the beginning of the study in response to unexpected severe toxicity. An initial high dose of 150 mg/kg/day was adjusted to 100 mg/kg/day for males during week 3, and a further decrease to 75 mg/kg/day was made for both sexes at the beginning of week 6. Both high-dose males and females were untreated during weeks 4 and 5 to allow for recovery. End points evaluated throughout the study included clinical observations (daily), body weight (weekly), and food consumption (weekly). Ophthalmoscopic examinations were performed prior to study start and just prior to study completion. Hematology (11 indices, including activated partial thromboplastin time), clinical chemistry (18 indices, including ALT, AST, GGTP, AP, and creatinine phosphokinase), and urinalysis (10 indices) were performed at month 6 and study completion (month 12). Organ weights, gross pathology, and histology were evaluated at month 12.

Mortality occurred the first 25 days of the study before dose reduction; exposure to 150 mg/kg/day caused one male dog to be sacrificed *in extremis* on day 12, one male death on day 25, and one female death on day 24 (Naylor and Stout 1996). A control male died on day 83, but all other dogs survived to the end of the study. Treatment-related clinical signs were primarily limited to severely affected high-dose dogs and the control male that died; these included hypoactivity, dehydration, decreased defecation, blood-like fecal color, emesis, emaciation, and/or pale oral mucosa. There were no significant group differences in mean body weight at the end of the study. Body weight gain was significantly reduced during the first month of the study, but recovered following dose reduction and adjustment of food availability. A mild anemia was observed at month 6 (significantly reduced red blood cells in females and HCT in males) at 75 mg/kg/day, but it resolved by the end of the study. The mild anemia correlated with histologic findings of bone marrow erythroid hyperplasia in females, and splenic excessive hematopoiesis and megakaryocyte proliferation in both sexes, indicating a compensatory response to the earlier anemia. Hepatic effects occurred at ≥50 mg/kg/day in both sexes as shown by changes in liver enzymes, increased liver weight, and histopathology. Effects on serum enzyme levels included significantly increased AP in males at 50 mg/kg/day at months 6 and 12 (731 and 620% higher than controls, respectively), females at 50 mg/kg/day at months 6 and 12 (525 and 330% higher), and females at 75 mg/kg/day at months 6 and 12 months (761 and 680% higher). Serum AP was also increased in males at 75 mg/kg/day after 6 and 12 months, but the changes were not statistically significant, possibly due to a reduced group size of 3 males at 75 mg/kg/day. Other clinical chemistry findings included significantly increased ALT in females at 75 mg/kg/day at month 12 (253% higher than controls), increased GGTP in females at

75 mg/kg/day at months 6 and 12 (131 and 161% higher), and decreased albumin in males at 50 and 75 mg/kg/day at month 6 (16 and 18% lower than controls) and females at 75 mg/kg/day at month 6 (19% lower). Absolute and relative liver weights were significantly increased (40–70% higher than controls) in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatocellular hypertrophy (diffuse or multifocal) occurred in all males and females at 50 and 75 mg/kg/day and in one female at 10 mg/kg/day. The study authors (Naylor and Stout 1996) considered the hepatocellular hypertrophy (multifocal) in the single 10 mg/kg/day female dog to be an adaptive response to a xenobiotic agent rather than a direct treatment related effect. Other liver lesions considered to be treatment-related included hepatocellular pigment deposition (two males and one female each at 50 and 75 mg/kg/day), bile duct/ductule hyperplasia (one male and one female at 75 mg/kg/day), and hepatic portal inflammation (periportal accumulation of neutrophils in one male at 50 mg/kg/day and two males at 75 mg/kg/day). Kidney effects included collecting duct epithelial vacuolation in one male at 75 mg/kg/day and at all dose levels in females (one each at 10 and 50 mg/kg/day and two at 75 mg/kg/day). The renal lesion was considered to be a possible effect of treatment at ≥50 mg/kg/day, because it was accompanied by increased relative kidney weight in females at ≥50 mg/kg/day and grossly observed renal discoloration in two females at 75 mg/kg/day. The highest chronic NOAEL and lowest LOAEL are 10 and 50 mg/kg/day, respectively, based on the hepatic effects in dogs (increased liver weight, changes in liver enzymes, and histopathology).

To derive a point of departure for MRL derivation, BMD analysis was performed on the serum AP level and relative liver weight data for the female dogs. The incidences of hepatocellular hypertrophy in the females (0/5, 1/5, 5/5, and 5/5 at 0, 10, 50, and 75 mg/kg/day) and males (0/5, 0/5, 5/5, and 5/5) are inappropriate for BMD modeling due to actual or effective responses of 0% in the control and low dose groups and 100% in the higher dose groups. The response in the low-dose female dog is effectively 0% because the authors implied that the hypertrophy in this single animal was not a hepatotoxic response. The incidences of the other dog liver lesions were not subjected to BMD analysis due to the low numbers of responders and group sizes. Continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to serum AP and relative liver weight data in the female dogs using a one standard deviation change from the control mean as the BMR. A summary of the predicted BMDs and BMDLs, as well as details of the BMD modeling, are presented in Appendix A. The relative liver weight data were judged to be unsuitable for BMD analysis due to inadequate modeling of variance. The best fit for the serum AP data was provided by the polynomial model, which resulted in a BMD_{1sd} of 15.40 mg/kg/day and a $BMDL_{1sd}$ of 12.32 mg/kg/day. The $BMDL_{1sd}$ of 12.32 mg/kg/day was rounded to one significant figure (10 mg/kg/day), adjusted for intermittent experimental exposure (5 days/7 days) to

give a duration-adjusted $BMDL_{1sd}$ of 7 mg/kg/day, and divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive a chronic-duration oral MRL of 0.07 mg/kg/day for 1,4-DCB.

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of dichlorobenzenes are indicated in Tables 3-1 and 3-5 and Figures 3-1 and 3-5.

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

Descriptive data are available from reports of humans exposed to 1,2- and 1,4-DCB by inhalation (and possibly dermal contact). It is important to note that the case studies discussed in this section should be interpreted with caution since they reflect incidents in which individuals have reportedly been exposed to 1,2- and 1,4-DCB, and they assume that there has been no other exposure to potentially toxic or infectious agents. There is usually little or no verification of these assumptions, and often no estimate of the level of exposure which may have occurred. With only rare exceptions, case studies in general are not scientifically equivalent to carefully designed epidemiological studies or to adequately controlled and monitored laboratory experiments. Thus, the case studies described below should be considered only as providing supplementary evidence that 1,2- and 1,4-DCB may cause the reported human effects. The highest NOAEL and all reliable LOAEL values after inhalation exposure to 1,2- and 1,4-DCB are recorded in Tables 3-1 and 3-2, respectively, and plotted in Figures 3-1 and 3-2, respectively. No LSE tables or figures were generated for 1,3-DCB due to a lack of inhalation data.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	6 hr				1532 M (14-day LC50)	Bonnet et al. 1982 1,2-dichlorobenzene	
2	Mouse (Sprague-Dawley)	6 hr				1236 (14-day LC50)	Bonnet et al. 1982 1,2-dichlorobenzene	
Systemic								
3	Rat (Sprague-Dawley)	4 hr	Hemato	29 M			Brondeau et al. 1990 1,2-dichlorobenzene	
4	Rat (NS)	10 d 6 hr/d	Hepatic	322			DuPont 1982 1,2-dichlorobenzene	
			Renal	322				
			Bd Wt		322 (slight body weight loss)			
5	Rat (Fischer- 344)	10 d Gd 6-18 6 hr/d	Bd Wt		100 F (reduced maternal body weight gain throughout gestation)		Hayes et al. 1985 1,2-dichlorobenzene	
6	Rat (albino)	0.5 hr (NS)	Hepatic		977 M (marked central lobular necrosis)		Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Renal		977 M (cloudy swelling of tubular epithelium)			

Table 3-1 Levels of Significant Exposure to 1,2-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL: Less Serious (ppm)	LOAEL: Serious (ppm)	Reference Chemical Form	Comments
7	Rat (albino)	1 hr (NS)	Hepatic		977 M (marked central lobular necrosis)		Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Renal		977 M (cloudy swelling of tubular epithelium)			
8	Rat (albino)	3 hr (NS)	Hepatic	539 M			Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Renal	539 M				
9	Rat (albino)	6.5 hr (NS)	Hepatic	539 M			Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Renal	539 M				
10	Mouse	4-14 d 5 d/wk 6 hr/d (NS)	Resp			64 M (moderate to severe nasal olfactory epithelial lesions)	Zissu 1995 1,2-dichlorobenzene	
11	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d	Bd Wt		100 F (slight maternal body weight loss on Gd 6-8 followed by recovery)		Hayes et al. 1985 1,2-dichlorobenzene	
Reproductive								
12	Rat (Fischer- 344)	10 d Gd 6-18 6 hr/d		400 F			Hayes et al. 1985 1,2-dichlorobenzene	

Table 3-1 Levels of Significant Exposure to 1,2-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
13	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d		400 F			Hayes et al. 1985 1,2-dichlorobenzene	
Developmental								
14	Rat (Fischer- 344)	10 d Gd 6-18 6 hr/d		200 F	400 F (delayed ossification of cervical vertebral centra)		Hayes et al. 1985 1,2-dichlorobenzene	
15	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d		400 F			Hayes et al. 1985 1,2-dichlorobenzene	
INTERMEDIATE EXPOSURE								
Systemic								
16	Rat (CD)	2 generations 7 hr/d 6 d/wk	Hepatic	50	150 (centrilobular hepatocellular hypertrophy in F0 and F1 adults)		Bio/dynamics 1989 1,2-dichlorobenzene	
			Bd Wt	50	150 (reduced body weight gain in F0 and F1 adults)			

Table 3-1 Levels of Significant Exposure to 1,2-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
17	Rat (albino)	6-7 mo 5 d/wk 7 hr/d (NS)	Resp	93 M			Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Cardio	93 M				
			Hepatic	93 M				
			Renal	93 M				
			Bd Wt	49 M	93 M (9.3% reduced body weight gain)			
18	Mouse (NS)	6.5 mo 5 d/wk 7 hr/d (NS)	Resp	49 F			Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Hepatic	49 F				
			Renal	49 F				
			Bd Wt	49 F				
19	Gn Pig (NS)	6-7 mo 5 d/wk 7 hr/d (NS)	Resp	93			Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Cardio	93				
			Hepatic	93				
			Renal	93				
			Bd Wt	93				

Table 3-1 Levels of Significant Exposure to 1,2-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
20	Rabbit (albino)	6-7 mo 5 d/wk 7 hr/d (NS)	Resp	93			Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Cardio	93				
			Hemato	93				
			Hepatic	93				
			Renal	93				
			Bd Wt	93				
Immuno/ Lymphoret								
21	Rat (albino)	6-7 mo 5 d/wk 7 hr/d (NS)		93			Hollingsworth et al. 1958 1,2-dichlorobenzene	
22	Gn Pig (NS)	6-7 mo 5 d/wk 7 hr/d (NS)			93 M (20% reduced absolute spleen weight)		Hollingsworth et al. 1958 1,2-dichlorobenzene	
Reproductive								
23	Rat (CD)	2 generations 7 hr/d 6 d/wk		394			Bio/dynamics 1989 1,2-dichlorobenzene	
24	Rat (albino)	6-7 mo 5 d/wk 7 hr/d (NS)		93 M			Hollingsworth et al. 1958 1,2-dichlorobenzene	

Table 3-1 Levels of Significant Exposure to 1,2-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
25	Gn Pig (albino)	6-7 mo 5 d/wk 7 hr/d (NS)		93 M			Hollingsworth et al. 1958 1,2-dichlorobenzene	

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

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gd = gestational day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to 1,2-dichlorobenzene - Inhalation

Acute (≤14 days)

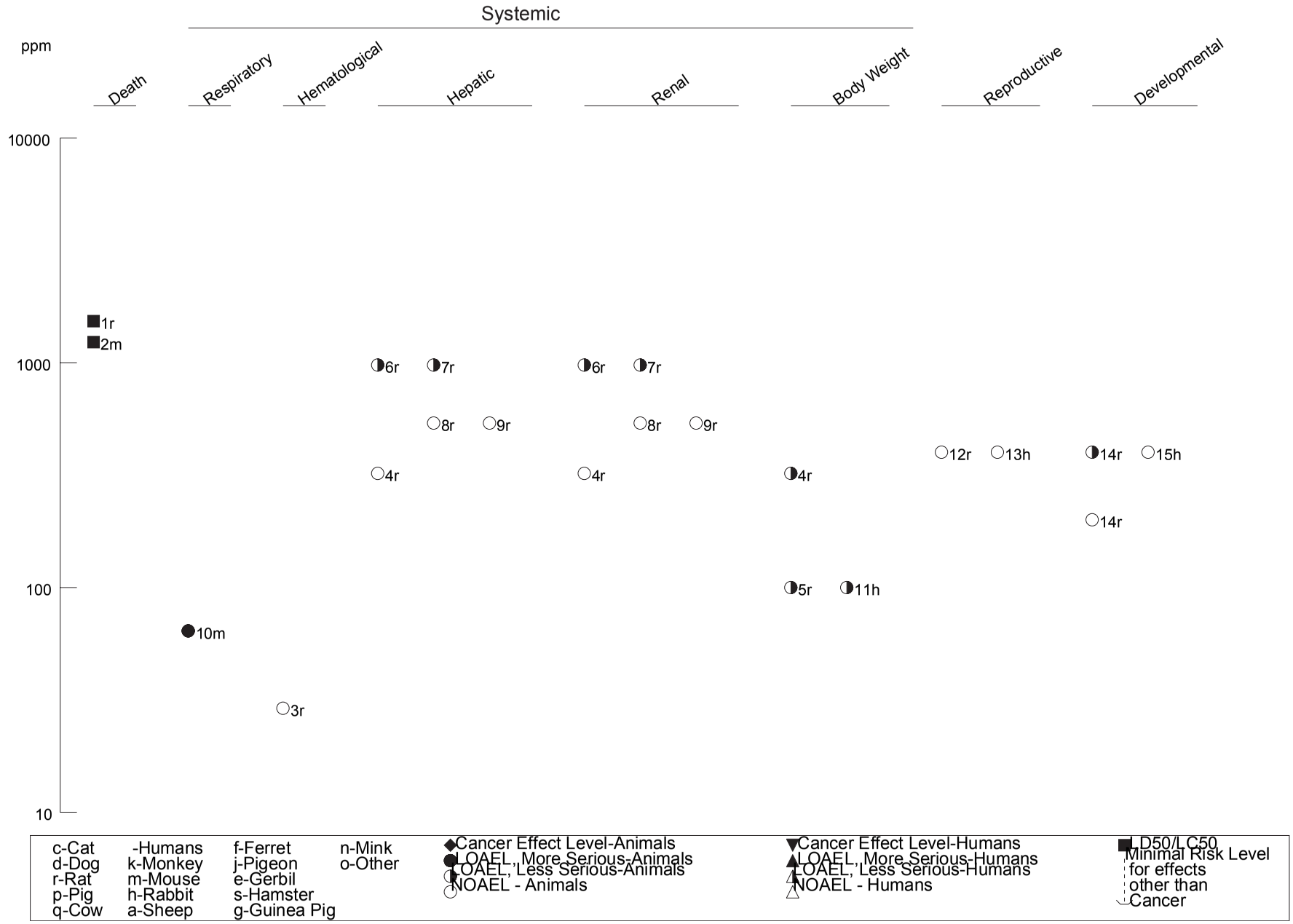


Figure 3-1 Levels of Significant Exposure to 1,2-dichlorobenzene - Inhalation *(Continued)*

Intermediate (15-364 days)

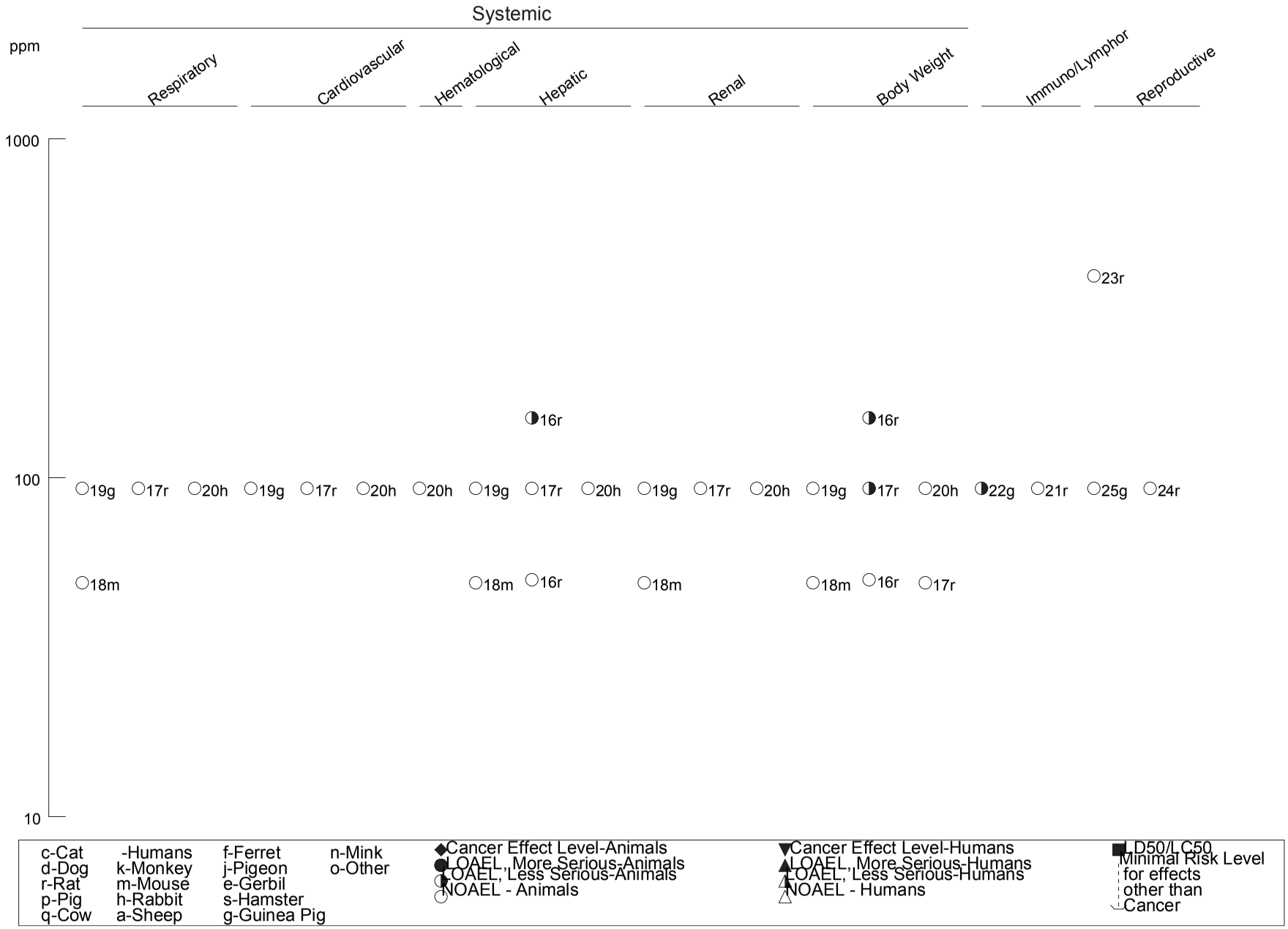


Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Human	4.75 yr 5 d/wk 8 hr/d (occup)	Resp	15 M[b]	30 M (minimal nose and eye irritation)	50 M (painful irritation of nose and eyes)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
2	Rat (Alderley-Park)	10 d Gd 6-15 6 hr/d	Resp	508 F			Hodge et al. 1977 1,4-dichlorobenzene	
			Cardio	508 F				
			Hepatic	508 F				
			Renal	508 F				
			Bd Wt	508 F				
3	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d	Bd Wt	300 F	800 F (slight maternal body weight loss on Gd 6-8 followed by recovery)		Hayes et al. 1985 1,4-dichlorobenzene	
Reproductive								
4	Rat (Alderley-Park)	10 d Gd 6-15 6 hr/d		500 F			Hodge et al. 1977 1,4-dichlorobenzene	
5	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d		800 F			Hayes et al. 1985 1,4-dichlorobenzene	
Developmental								
6	Rat (Alderley-Park)	10 d Gd 6-15 6 hr/d		508 F			Hodge et al. 1977 1,4-dichlorobenzene	

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
7	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d		300 F	800 F (increased incidence of retroesophageal right subclavian artery)		Hayes et al. 1985 1,4-dichlorobenzene	
INTERMEDIATE EXPOSURE								
Death								
8	Rat (NS)	9-12 wk 5 d/wk 8 hr/d				798 (2/19 males and 2/15 females died)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
9	Gn Pig (NS)	4-4.5 wk 5 d/wk 8 hr/d				798 M (2/16 died)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
10	Rabbit (NS)	12 wk 5 d/wk 8 hr/d				798 (3 males and 1 female died)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
Systemic								
11	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp	600			Aiso et al. 2005a 1,4-dichlorobenzene	
			Hepatic	120 M	270 M (increased liver weight, serum cholesterol, and serum phospholipids)			
			Bd Wt	600				

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
12	Rat (NS)	2-12 wk 5 d/wk 7 or 8 hr/d	Resp	798 F		173 M (slight interstitial edema, alveolar hemorrhage)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Cardio	173				
			Hepatic		173 F (slight liver congestion and granular degeneration)	798 (cloudy swelling and central necrosis)		
			Renal		173 (increased relative kidney weight)			
			Ocular		798 (eye irritation)			
			Bd Wt	173	798 (unquantitated weight loss)			
13	Rat (NS)	5.1-7.1 mo 5 d/wk 7 hr/d	Hemato	96			Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Hepatic	96	158 (increased relative liver weight; cloudy swelling or degeneration of parenchyma)			
			Renal	96	158 M (increased relative kidney weight)			
			Bd Wt	341				

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	2 generations	Resp	211	538		Tyl and Neeper-Bradley 1989 1,4-dichlorobenzene	
			Hepatic	66[c] M	211[d] M (increased liver weight)			
				211 F	538 F			
			Renal	538 F				
			Ocular	211	538 (encrustation of periocular region; lacrimation)			
			Bd Wt	66[d] M 211 F	211[d] M (decreased body weight in the male F0 group and in the F1 male and females in the 5-week recovery study)			
					538 F			
			Other	211	538 (decreased grooming; unkempt appearance; decreased food consumption)			

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
15	Mouse BDF1	13 wk 5 d/wk 6 hr/d	Resp	600			Aiso et al. 2005a 1,4-dichlorobenzene	
			Hemato	600				
			Hepatic	120 M	270 M (increased relative liver weight and serum ALT)			
			Renal	600				
			Bd Wt	600				
16	Mouse (NS)	5.1-7.1 mo 5 d/wk 7 hr/d	Hepatic	158 M 96[d] F			Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Renal	158 M 96[d] F				
			Bd Wt	158 M 96[d] F				
17	Gn Pig (NS)	5.1-7.1 mo 5 d/wk 7 hr/d	Hepatic	96	158 F (increased relative liver weight)	341 (focal necrosis, slight cirrhosis in males)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Renal	341				
			Bd Wt	96	158 (slight depression in final body weight)			

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
18	Gn Pig (NS)	2-4.5 wk 5 d/wk 7 or 8 hr/d	Resp		173 F (alveolar hemorrhage and edema)		Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Cardio	798				
			Hepatic	173		798 (cloudy swelling in the liver and central necrosis)		
			Renal	798				
			Ocular	173	798 (eye irritation)			
			Bd Wt	173	798 (body weight loss, not quantified)			
19	Rabbit (NS)	2-12 wk 5 d/wk 7 or 8 hr/d	Resp		173 F (lung congestion and interstitial edema)	798 (emphysema in 2/8)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Hepatic	173		798 (cloudy swelling in the liver and central necrosis)		
			Renal	798				
			Ocular		798 (eye irritation; reversible nonspecific eye changes)			
			Bd Wt	173	798 (decreased body weight gain, not quantitated)			

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
Immuno/ Lymphoret									
20	Gn Pig (Hartley)	12 wk		50 M				Suzuki et al. 1991 1,4-dichlorobenzene	
Neurological									
21	Rat (NS)	9-12 wk 5 d/wk 8 hr/d				798	(tremors, weakness, unconsciousness)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
22	Rat	2 generations		211		538	(tremors and other signs of neurotoxity in F0 and F1 adults)	Tyl and Neeper-Bradley 1989 1,4-dichlorobenzene	
23	Gn Pig (NS)	4-4.5 wk 5 d/wk 8 hr/d				798	(tremors, weakness, unconsciousness)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
24	Rabbit (NS)	12 wk 5 d/wk 8 hr/d				798	(tremors, weakness, unconsciousness)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
Reproductive									
25	Rat (NS)	5.1-7.1 mo 5 d/wk 7 hr/d		158 M				Hollingsworth et al. 1956 1,4-dichlorobenzene	
26	Rat (NS)	16 d 5 d/wk 7 hr/d		173 M				Hollingsworth et al. 1956 1,4-dichlorobenzene	
27	Rat (Sprague-Dawley)	2 generations		538				Tyl and Neeper-Bradley 1989 1,4-dichlorobenzene	

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
28	Gn Pig (NS)	16 d 5 d/wk 7 hr/d		173 M			Hollingsworth et al. 1956 1,4-dichlorobenzene	
29	Gn Pig (NS)	5.1-7.1 mo 5 d/wk 7 hr/d		158 M			Hollingsworth et al. 1956 1,4-dichlorobenzene	
Developmental								
30	Rat (Sprague-Dawley)	2 generations		93 211		538 (increased stillbirths and reduced postnatal survival in F1 and F2 pups)	Tyl and Neeper-Bradley 1989 1,4-dichlorobenzene	
CHRONIC EXPOSURE								
Death								
31	Rat (Fischer- 344)	104 wk 5 d/wk 6 hr/d chamber				300 M (30% reduced survival)	Aiso et al. 2005b 1,4-dichlorobenzene	

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Systemic								
32	Rat (Fischer- 344)	104 wk 5 d/wk 6 hr/d chamber	Resp	75 M 20[e] F	300 M (eosinophilic changes in olfactory epithelium) 75[d] F (eosinophilic changes in nasal olfactory epithelium)		Aiso et al. 2005b 1,4-dichlorobenzene	
			Renal	75 M	300 M (mineralization of renal papilla, urothelial hyperplasia)			
			Bd Wt	300				
33	Mouse Crj:BDF1	104 wk 5 d/wk 6 hr/d chamber	Resp	75 F	300 F (metaplasia in nasal olfactory epithelium)		Aiso et al. 2005b 1,4-dichlorobenzene	
			Hepatic	75[d] M 300 F	300 M (centrilobular hepatocellular hypertrophy)			
			Bd Wt	75	300 (reduced terminal body weight)			
Reproductive								
34	Rat (Fischer- 344)	104 wk 5 d/wk 6 hr/d chamber		300			Aiso et al. 2005b 1,4-dichlorobenzene	

Table 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
35	Mouse Crj:BDF1	104 wk 5 d/wk 6 hr/d chamber		300			Aiso et al. 2005b 1,4-dichlorobenzene	
Cancer								
36	Mouse Crj:BDF1	104 wk 5 d/wk 6 hr/d chamber				300 M (CEL: hepatocellular carcinoma, hepatic histiocytic sarcoma) 300 F (CEL: bronchoalveolar adenoma and carcinoma) 10 F (CEL: hepatocellular adenoma and carcinoma)	Aiso et al. 2005b 1,4-dichlorobenzene	

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

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 2 ppm. The MRL was obtained by dividing the NOAEL by an uncertainty factor of 10 (for human variability).

c Study result used to derive an intermediate-duration inhalation Minimal Risk Level (MRL) of 0.2 ppm for 1,4-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on liver weight to select a point of departure, which was adjusted for intermittent exposure and converted to a Human Equivalent Concentration (HEC), then divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

d Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

e Study result used to derive a chronic-duration inhalation Minimal Risk Level (MRL) of 0.01 ppm for 1,4-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on incidences of nasal lesions to select a point of departure, which was adjusted for intermittent exposure and converted to a Human Equivalent Concentration, then divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using a dosimetric adjustment and 10 for human variability).

ALT = alamine aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = Female; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation

Acute (≤14 days)

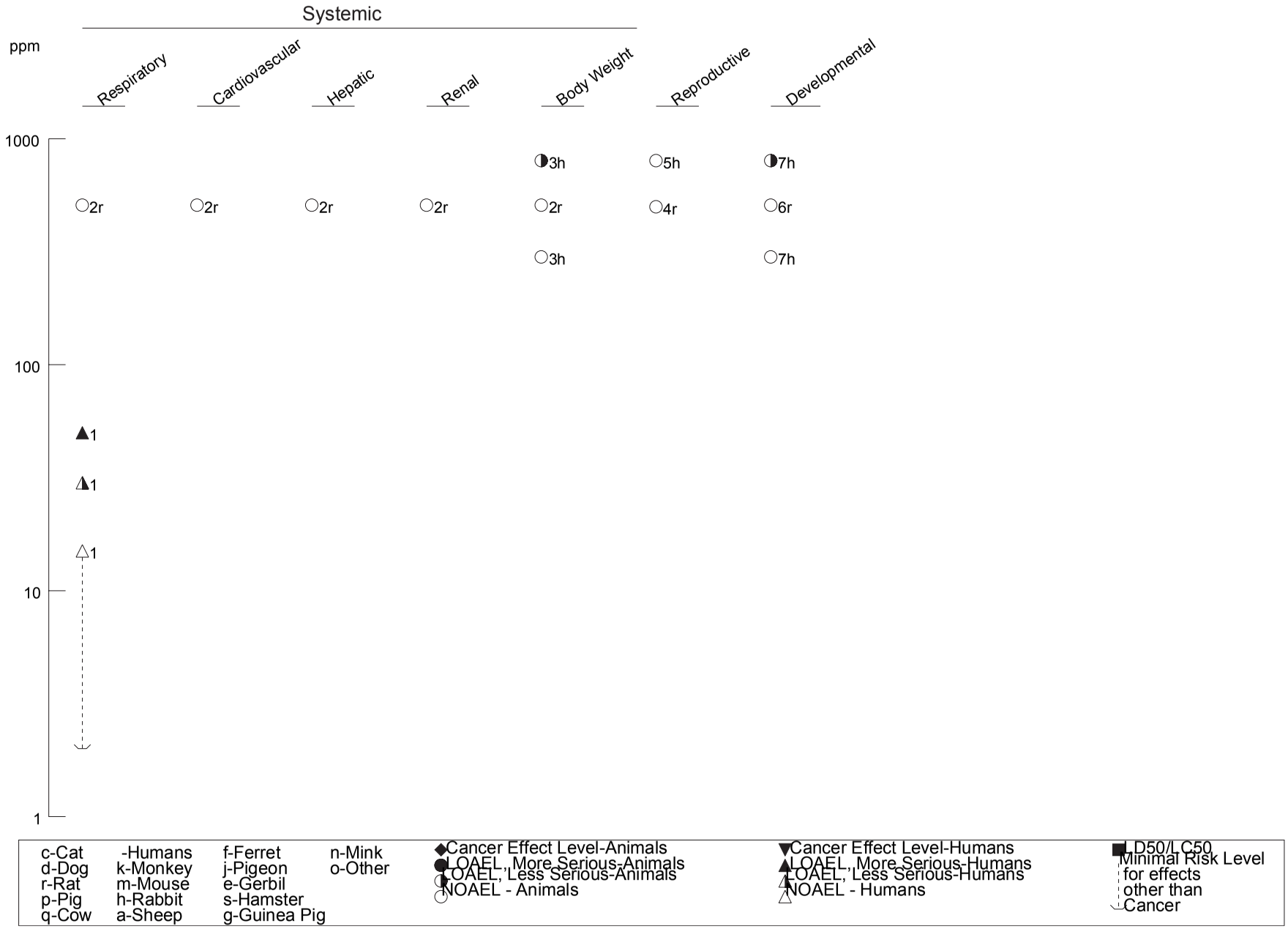


Figure 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation *(Continued)*

Intermediate (15-364 days)

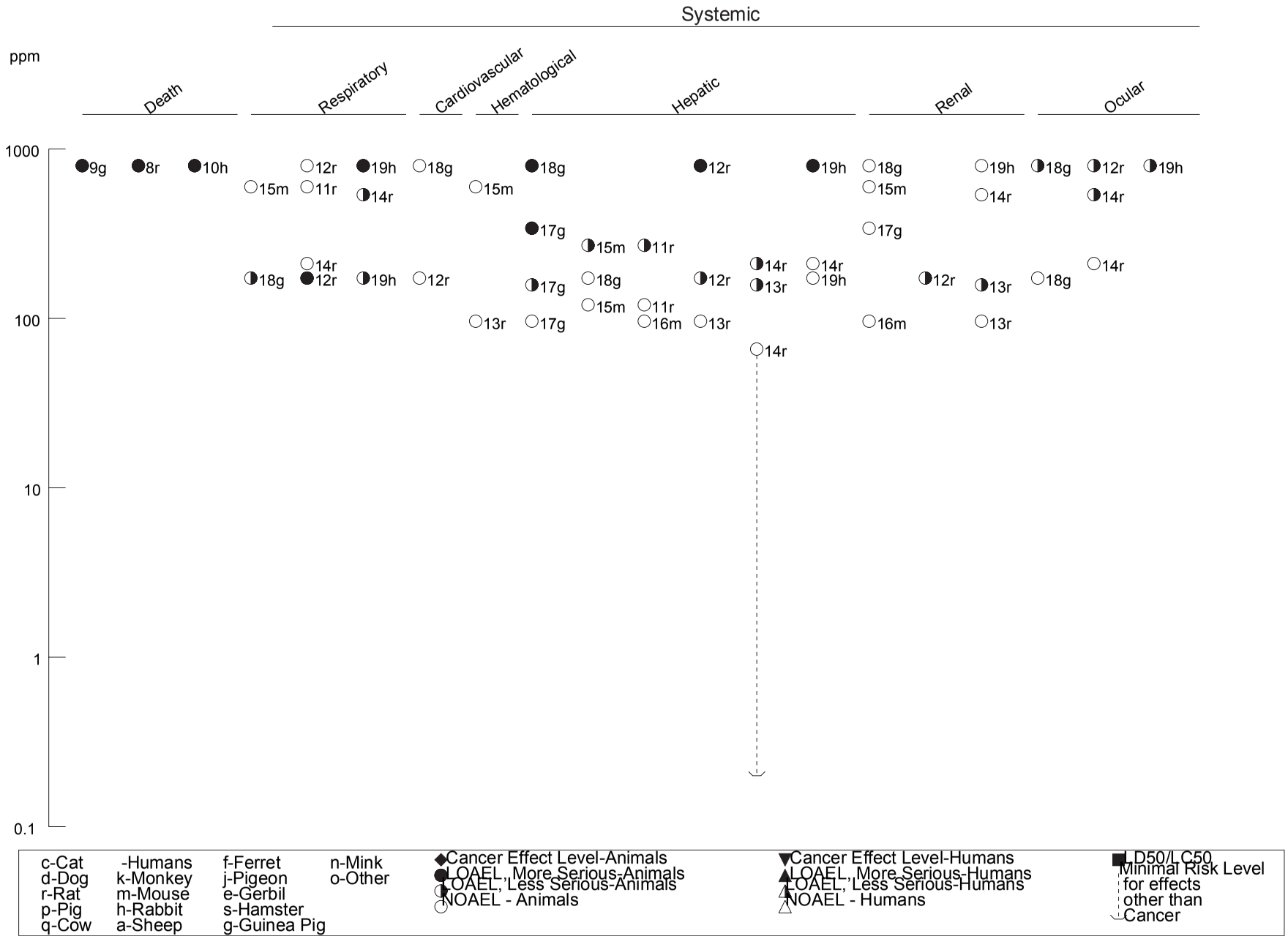


Figure 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation *(Continued)*

Intermediate (15-364 days)

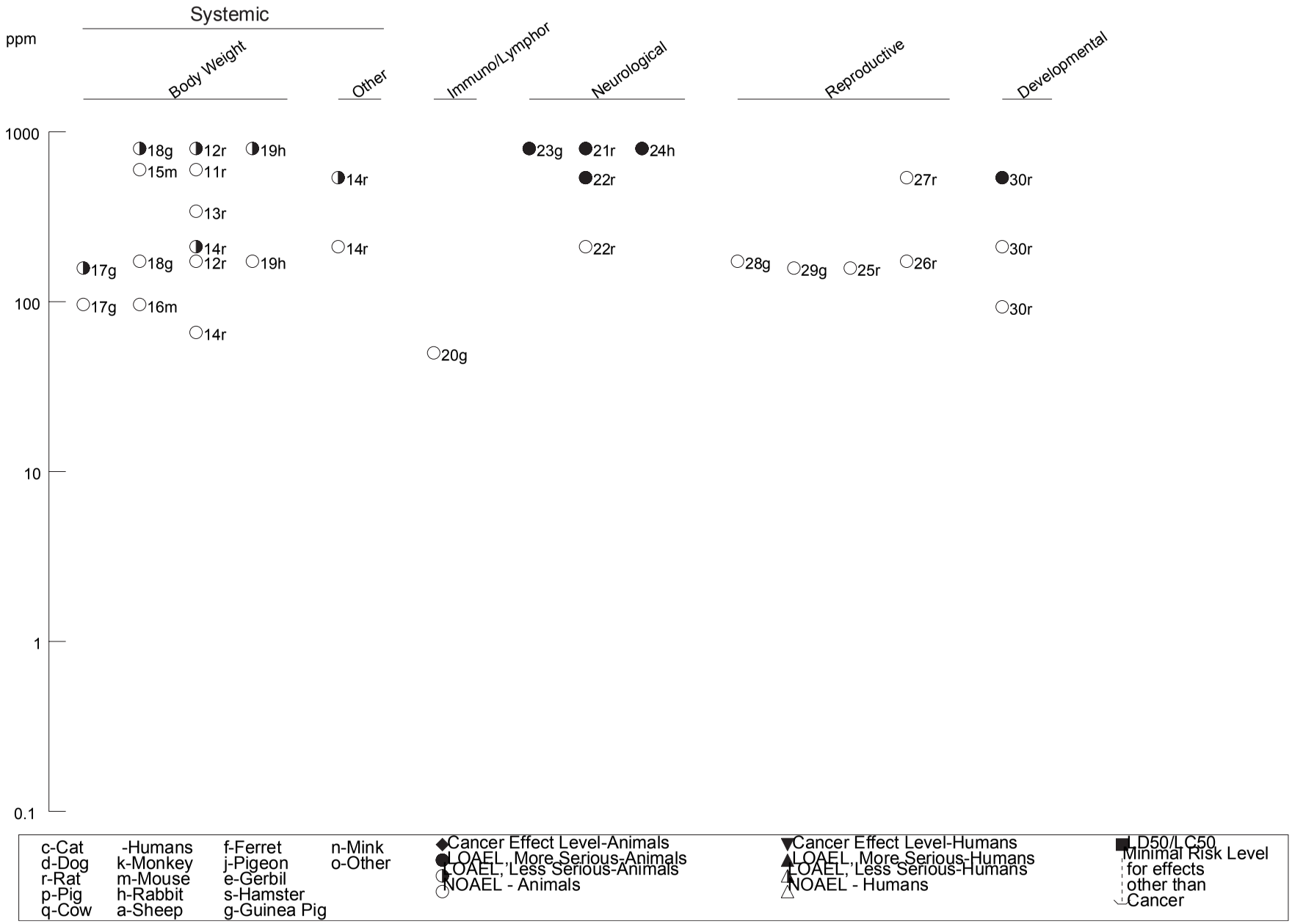
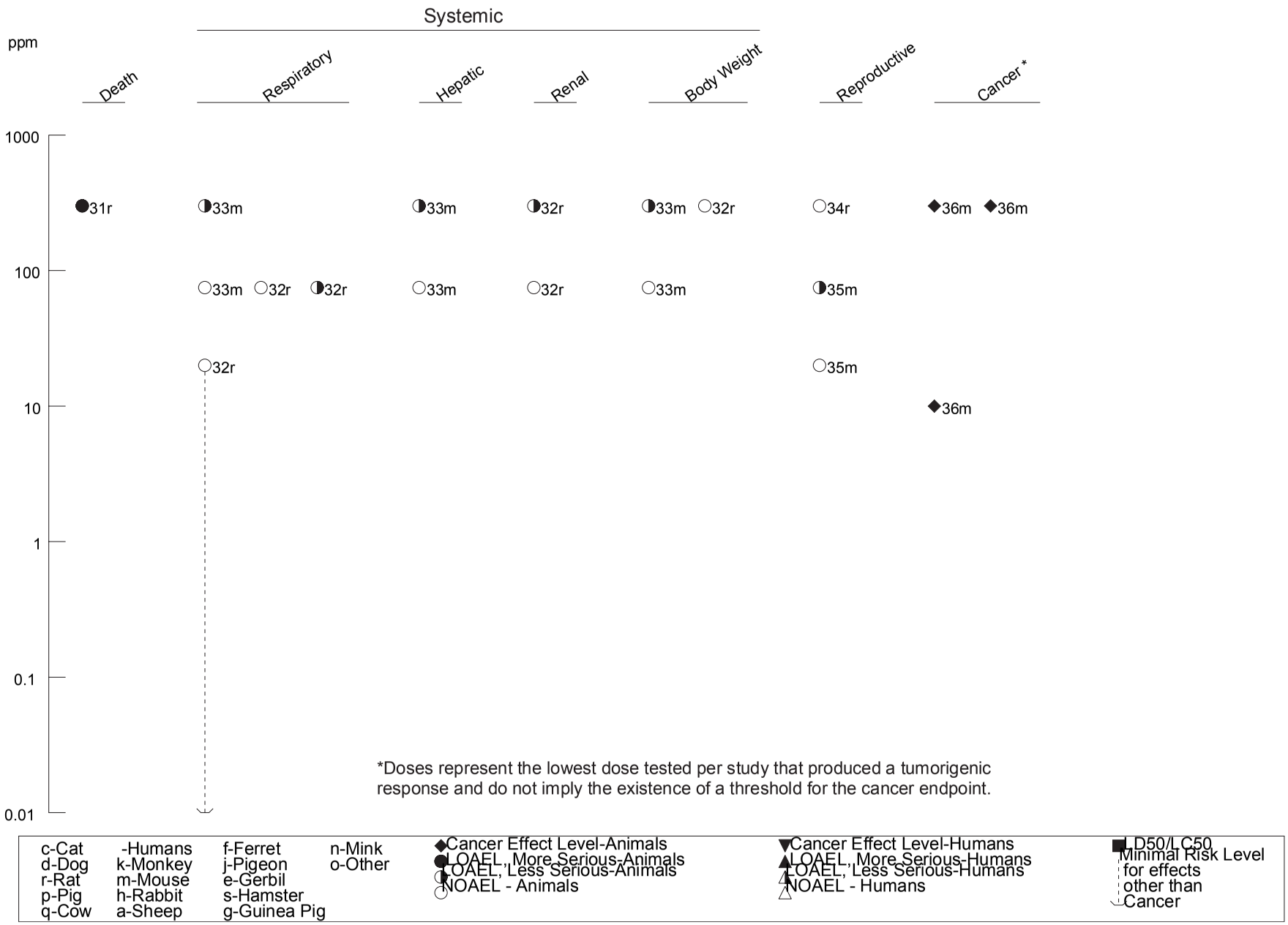


Figure 3-2 Levels of Significant Exposure to 1,4-dichlorobenzene - Inhalation

Chronic (≥365 days)



3.2.1.1 Death

1,2-Dichlorobenzene. No studies were located regarding death in humans following inhalation exposure to 1,2-DCB.

Inhalation LC_{50} values of 1,532 and 1,236 ppm were determined for rats and mice, respectively, that were exposed to 1,2-DCB for 6 hours and observed for the following 14 days (Bonnet et al. 1982). No mortality was observed in rats that were exposed to 1,2-DCB in concentrations of 977 ppm for 0.5–1 hour or 539 ppm for 3 hours (Hollingsworth et al. 1958).

1,3-Dichlorobenzene. No studies were located regarding death in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. Only one report of human death attributed to 1,4-DCB inhalation exposure has been located in the literature. A 60-year-old man and his wife died within months of each other due to acute yellow atrophy of the liver (also known as massive hepatic necrosis or fulminant hepatitis; diagnosis was not verified histologically) (Cotter 1953). Their home had been "saturated" with 1,4-DCB moth ball vapor for a period of about 3–4 months, but no air measurements were available. Clinical symptoms included severe headache, diarrhea, numbness, clumsiness, slurred speech, weight loss (50 pounds in 3 months in the case of the husband), and jaundice. The wife died within a year of the initial exposure; however, it was not clear if 1,4-DCB was the primary cause of death. This case study did not address whether these individuals consumed excessive amounts of alcohol or had previous medical problems, such as a chronic liver infection.

Several studies were located regarding death in animals after inhalation exposure to 1,4-DCB. In an acute-duration study, two of six male CD-1 mice exposed to 1,4-DCB at an air concentration of 640 ppm, 6 hours/day for 5 days died on the fifth day; no deaths were reported at an exposure level of 320 ppm (Anderson and Hodge 1976).

Mortality data were also reported in intermediate-duration studies using rats, guinea pigs, and rabbits. In studies performed by Hollingsworth et al. (1956), rats, guinea pigs, and rabbits were exposed to 1,4-DCB vapors for 9–12 weeks at an air concentration of 798 ppm, 8 hours/day, 5 days/week. In that study, 4 of 34 rats, 2 of 23 guinea pigs, and 4 of 16 rabbits died during the study period. The exact number of exposures that resulted in death was not specified.

In a chronic-duration study, there was no evidence of a treatment effect on mortality in Wistar rats exposed to 1,4-DCB at concentrations up to 490–499 ppm for 5 hours/day, 5 days/week for 76 weeks (Riley et al. 1980a).

Another chronic study found that survival was significantly reduced in male rats (F344/DuCrj) that were exposed 300 ppm 1,4-DCB for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Survival in the male rats was noticeably lower than controls beginning at approximately study week 80, and terminal survival in the 0, 20, 75, and 300 ppm groups of the study were 66% (33/50), 68% (34/50), 58% (29/50), and 36% (18/50), respectively. There were no effects on survival in similarly exposed female rats. Male mice (Crj:BDF_1) that were similarly exposed to the same levels of 1,4-DCB had slightly reduced survival at all levels of exposure (80% [39/49], 63% [31/49], 64% [32/50], and 61% [30/49] at 0, 20, 75, and 300 ppm, respectively), but the decreases were not significantly different from controls or dose-related. Survival in female mice was similar to controls.

3.2.1.2 Systemic Effects

Respiratory Effects.

1,2-Dichlorobenzene. Periodic industrial hygiene surveys and medical examinations were conducted in a plant where an unreported number of men were exposed to 1,2-DCB at an average level of 15 ppm (range 1–44 ppm) for an unreported duration (Hollingsworth et al. 1958). No nasal or eye irritation was attributable to exposure. Additionally, Hollingsworth et al. (1958) noted that his researchers detected 1,2-DCB odor at a concentration of 50 ppm without eye or nasal irritation during repeated vapor inhalation experiments on animals. An earlier source (Elkins 1950) referenced by Hollingsworth (1958) reported that occupational exposure to 100 ppm of 1,2-DCB caused irritation of the eyes and respiratory passages.

No changes in absolute lung weight or lung histology were reported in rats (20/sex), guinea pigs (8/sex), rabbits (2/sex), or monkeys (2 females) exposed to 93 ppm 1,2-DCB for 7 hours/day, 5 days/week for 6–7 months, or in mice (10 females) similarly exposed to 49 ppm 1,2-DCB (Hollingsworth et al. 1958). Relative lung weight was not determined. The scope of histological evaluations was not specifically reported; organs that were weighed are inferred to have been histologically examined.

Histological examinations of the upper and lower respiratory tract were conducted in groups of 10 male Swiss OF1 mice that were exposed to 1,2-DCB in actual mean concentrations of 0, 64, or 163 ppm (0, 385, or 980 mg/m^3) for 6 hours/day, 5 days/week for 4, 9, or 14 days (Zissu 1995). Histological examinations were performed on the upper and lower respiratory tracts. Nonrespiratory tissues were not evaluated. Histopathologic lesions were observed in the olfactory epithelium of the nasal cavity at ≥64 ppm. The olfactory epithelial lesions were graded as very severe following the 4-day exposure and moderate after the 14-day exposure, indicating to the authors that a repair mechanism may take place despite continued exposure. The more severe cases were characterized by a complete loss of olfactory epithelium, which left only the partially denuded basement membrane. No histological alterations were observed in the respiratory epithelium of the nasal cavity, or in the trachea or lungs. The results suggest that the upper respiratory tract is a target for inhalation exposures to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding respiratory effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. A case of pulmonary granulomatosis was reported to have occurred in a 53-year-old woman who, for 12–15 years, had been inhaling 1,4-DCB crystals that were scattered on a weekly basis on the carpets and furniture of her home. A lung biopsy revealed the presence of 1,4-DCB crystals with the surrounding lung parenchyma being distorted by fibrosis, thickening of the alveolar walls, and marked infiltrates of lymphocytes and mononuclear phagocytes. Also, there was some thickening of the muscular walls of small arteries and focal fibrous thickening of the pleura (Weller and Crellin 1953). These effects are most likely related to the physical interaction of 1,4-DCB crystals (or any crystals when inhaled) with lung tissue, rather than to chemical toxicity. This conclusion by the authors of the study was based on exposure history of the patient, radiography, and histological examination of the lung tissue which showed the presence of birefringent crystals and a clear granulatomous reaction.

A study of 58 men occupationally exposed for 8 hours/day, 5 days/week, continually or intermittently, for 8 months to 25 years (average, 4.75 years) to 1,4-DCB found that the odor was faint at 15–30 ppm and strong at 30–60 ppm (Hollingsworth et al. 1956). Painful irritation of the nose and eyes was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. At levels >160 ppm, the air was considered not breathable for unacclimated persons. The results of this study indicate that nose and eye irritation are critical effects of acute and repeated exposures to 1,4-DCB in humans. Because odor detection is a warning property expected to

prevent irritation caused by 1,4 DCB (Hollingsworth et al. 1956), 15 ppm was designated a NOAEL for irritant effects and used to derive an MRL of 2 ppm for acute inhalation exposure to 1,4-DCB.

Associations between blood concentrations of 1,4-DCB and 10 other volatile organic compounds (VOCs) and pulmonary function were evaluated in 953 adult participants in the Third National Health and Nutrition Examination Survey (NHANES III) (1988–1994) of the general population who had both blood VOC and pulmonary function measurements (Elliot et al. 2006). The mean age of the subjects was 36.6 years (range 20–59), 43.1% were female, and 26.3% were current smokers. Pulmonary function measures included forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), and maximum mid-expiratory flow rate (MMEFR). Least squares regression models were used to evaluate the association between each VOC and each pulmonary function outcome. The models used natural log transformations of VOC concentrations, and were adjusted for race/ethnicity, age, standing height, body mass index, sex, smoking, and emphysema to account for differences in pulmonary function based on these characteristics. In the models unadjusted for smoking variables, reductions in at least one pulmonary function outcome were statistically significant for 1,4-DCB, benzene, ethylbenzene, styrene, and toluene. When the models were adjusted for smoking variables, 1,4-DCB was the only VOC that was statistically significantly associated with reduced pulmonary function. Among all 1,4-DCB participants (n=846), there was a statistically significant ($p<0.05$) inverse relationship between 1,4-DCB level and FEV_1 and MMEFR. The linear regression coefficient (β) was -96 mL (95% CI -182 to -11) for FEV_1 and -198 mL/sec (95% CI -388 to -8) for MMEFR. The β coefficient estimates the expected change in lung function as the concentration of 1,4-DCB increases from the 10th to 90th percentile (3.76 μg/L) on the natural log scale. Analysis by race and sex showed statistically significant results for FEV_1 in non-Hispanic white females [β=-266 mL (95% CI -488 to -43)] and African-American males [β=-282 mL (95% CI -497 to -66)]. Analyses conducted in 534 subjects using urinary concentrations of 1,4-DCB and its major metabolite, 2,5-dichlorophenol, showed statistically significant β coefficients for FEV_1 for both 1,4-DCB (-96 mL, 95% CI not reported) and 2,5-dichlorophenol (-134 mL, 95% CI not reported). Analyses were also performed using non-logarithmically transformed blood concentrations of 1,4-DCB that were categorized into deciles. Tests for linear trend across deciles were statistically significant for FEV_1 and MMEFR. Compared with subjects in the lowest decile of 1,4-DCB concentration (0.10 ppb), subjects in the highest decile (>4.40 ppb) had FEV_1 decrements of -153 mL (95% CI -297 to -8) and MMEFR decrements of -346 mL/sec (95% CI -667 to -24). The authors concluded that the findings of this study suggest that exposure to 1,4-DCB at levels found in the general population may result in decreases in lung function.

In pregnant Alderley-Park rats, whole-body exposure to 1,4-DCB at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours/day on gestation days (Gd) 6–15 produced no adverse clinical or pathological signs in the lung tissues of the dams (Hodge et al. 1977). Mild histopathological changes of interstitial edema, congestion, and alveolar hemorrhage were observed in the lungs of male (but not female) rats, female guinea pigs, and one female rabbit after 16 days of exposure to 1,4-DCB at 173 ppm (Hollingsworth et al. 1956). Congestion and emphysema were also reported in the lungs of two rabbits exposed to 798 ppm for 12 weeks (Hollingsworth et al. 1956). These observations were derived from a large study using several species of laboratory animals; however, interspecies comparisons are difficult to make due to the various experimental designs used in this study. For example, at 798 ppm, 10 male rats, 15 female rats, 16 male guinea pigs, seven female guinea pigs, and 8 rabbits of each sex were exposed up to 62 times; at 173 ppm, five rats of each sex, five guinea pigs of each sex, and one rabbit of each sex were exposed for 16 days. These reported observations provide only qualitative evidence of respiratory effects as a result of intermediate-duration inhalation exposure to 1,4-DCB.

An intermediate-duration study was conducted in which F344 rats and BDF_1 mice were chamber–exposed to 25, 55, 120, 270, or 600 ppm of 1,4-DCB for 6 hours/day, 5 days/week for 13 weeks (Aiso et al. 2005a). No histological changes in the respiratory tract were reported. This study apparently conformed to (OECD) (1981) testing guidelines for a 90-day inhalation toxicity study, indicating that the histological examinations included naso-pharyngeal tissues and lungs.

In a chronic-duration study, male and female Wistar rats were exposed to 1,4-DCB at air concentrations of 75 or 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks (Riley et al. 1980a). Rats in the high-exposure group showed a small but significant increase in absolute lung weight at termination of the study (112 weeks). This response was not observed in rats sacrificed on week 76 or in rats exposed to 75 ppm 1,4-DCB for 112 weeks. No treatment-related histological alterations were observed in the larynx, trachea, or lungs in this study.

Another chronic inhalation study was conducted in which groups of 50 male and female F344/DuCrj rats, and 50 male and 50 female Crj:BDF_1 mice, were exposed to 1,4-DCB in concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Histological examinations of the respiratory tract (nasal cavity, trachea, and lung) showed nasal epithelial effects in rats and mice. The nasal lesions in rats mainly included eosinophilic changes of moderate or greater severity in the olfactory epithelium in male rats at 300 ppm and female rats at ≥75 ppm. Incidences of this lesion at 0, 20, 75, and 300 ppm were 1/50, 2/50, 2/50, and 7/50 in the male

rats, and 28/50, 29/50, 39/50, and 47/50 in the female rats. The increases were significantly ($p \leq 0.05$) different than the control values and there was a trend of increasing response with increasing dose in both sexes. Additionally observed were significantly increased incidences of eosinophilic changes of the respiratory epithelium and respiratory metaplasia in the 300 ppm female rats only. The nasal lesions in mice included significantly increased incidences of respiratory metaplasia in the nasal gland (moderate severity) in males at 75 ppm (9/49, 12/49, 18/50, 11/49) and olfactory epithelium (slight severity) in males at 75 ppm (23/49, 30/49, 37/50, 22/49) and females at 300 ppm (7/50, 6/50, 2/49, 20/50), but the effects in the males were not dose-related (i.e., incidences were increased at 75 ppm but not at 300 ppm). The nasal lesions in female rats, the more sensitive species and sex, were selected as the critical effect for deriving a chronic-duration inhalation MRL of 0.01 ppm for 1,4-DCB.

Cardiovascular Effects.

1,2-Dichlorobenzene. No studies were located regarding cardiovascular effects in humans following inhalation exposure to 1,2-DCB.

No changes in absolute heart weight or heart histology were reported for rats (20/sex), guinea pigs (8/sex), rabbits (2/sex), or monkeys (2 females) following exposure to 93 ppm 1,2-DCB for 7 hours/day, 5 days/week for 6–7 months, or in mice (10 females) that were similarly exposed to 49 ppm 1,2-DCB (Hollingsworth et al. 1958). Relative heart weight was not determined. The scope of histological evaluations was not specifically reported; organs that were weighed are inferred to have been histologically examined.

1,3-Dichlorobenzene. No studies were located regarding cardiovascular effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding cardiovascular effects in humans following inhalation exposure to 1,4-DCB.

Limited information is available regarding cardiovascular effects in animals. No alterations in relative heart weight were observed in rats or guinea pigs exposed to 1,4-DCB at an air concentration of 173 ppm, 7 hours/day, 5 days/week for up to 12 exposures (Hollingsworth et al. 1956). Similar results were reported after approximately 130 exposures to 1,4-DCB at an air concentration of 96 ppm using the same

exposure protocol (Hollingsworth et al. 1956); no other cardiovascular end points were evaluated in this study.

In pregnant Alderley-Park rats, whole-body exposure to 1,4-DCB at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours/day from Gd 6 to 15 produced no adverse clinical or pathological signs in the heart tissues of the dams (Hodge et al. 1977).

A significant increase in absolute heart weight was reported in male and female rats exposed to 1,4-DCB at air concentrations of 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks and allowed to recover until week 112 (Riley et al. 1980a). This effect was not seen at the 76-week interim sacrifice or at the lower-exposure concentration of 75 ppm. Examination of the heart and aorta at interim sacrifices or at termination of the study revealed no significant histological alterations related to 1,4-DCB treatment.

Gastrointestinal Effects.

1,2-Dichlorobenzene. No studies were located regarding gastrointestinal effects in humans or animals following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding gastrointestinal effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. Two case reports provide evidence of gastrointestinal effects in humans after exposure to unknown concentrations of 1,4-DCB. A 60-year-old man who had been exposed to vapors of 1,4-DCB in his home for 3–4 months reported having several bowel movements a day with loose tarry stools for 10 days before being admitted to a hospital (Cotter 1953). The second case is that of a 34-year-old woman who had been exposed to vapors of 1,4-DCB at work and became acutely ill with nausea and vomiting, and was hospitalized with hemorrhage from the gastrointestinal tract (Cotter 1953). The physical and chemical findings led to the diagnosis of subacute yellow atrophy and cirrhosis of the liver from 1,4-DCB exposure. No further information was located.

Limited information regarding gastrointestinal effects in animals is provided in a chronic-duration study. In that study (Riley et al. 1980a), the investigators found no effect on the organ weight or on gross and histopathological appearance of the caecum, colon, duodenum, jejunum, esophagus, pancreas, and

stomach in male and female Wistar rats exposed to 1,4-DCB at air concentrations of up to 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks.

Hematological Effects.

1,2-Dichlorobenzene. Periodic industrial hygiene surveys and medical examinations were conducted in a plant where an unreported number of men were exposed to 1,2-DCB at an average level of 15 ppm (range 1–44 ppm) for an unreported duration (Hollingsworth et al. 1958). No effects on clinical hematology indices (red blood cell count, total and differential white blood cell counts, hemoglobin, hematocrit, and mean corpuscular volume) were attributable to exposure.

Red blood cell (RBC), total white blood cell (WBC), and leucocyte differential cell counts were assessed in groups of five male Sprague-Dawley rats that were exposed to 0, 5, 10, 16, or 29 ppm 1,2-DCB for 4 hours (Brondeau et al. 1990). Total WBC counts were significantly ($p \leq 0.05$) reduced at ≥10 ppm without any changes in WBC differential or RBC counts. The effect of 1,2-DCB on total WBC count was further assessed in groups of 10 male Sprague-Dawley rats that were normal or adrenalectomized and exposed to 0 or 24 ppm for 4 hours. Adrenalectomy caused a significant increase in total WBCs (39.9% higher than normal controls), although exposure did not significantly affect WBC count in the adrenalectomized rats. Because the adrenal-dependent leucopenia was similar to that observed after exposure to various irritant stressors, and is thought to be a secondary manifestation of increased secretion of glucocorticosteroids, the authors considered the effect to be an associative response to sensory irritation.

No hematological changes were reported in rabbits (2/sex) or monkeys (2 females) that were exposed to 93 ppm 1,2-DCB for 7 hours/day, 5 days/week for 6–7 months (Hollingsworth et al. 1958). The hematology end points that were evaluated were not specified.

1,3-Dichlorobenzene. No studies were located regarding hematological effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. Two reports of hematological effects in humans after inhalation exposure to 1,4-DCB were located in the literature. Based on results from blood counts, anemia was diagnosed in two men; one had been exposed to unknown concentrations of 1,4-DCB vapors at home for 3–4 months and the other had been in a storage plant saturated with 1,4-DCB vapor. A woman exposed in a similar

manner was diagnosed with borderline anemia (Cotter 1953). Early industrial hygiene surveys found no evidence of adverse hematological effects attributable to exposure to 1,4-DCB in workers at air concentrations ranging from 10 to 550 ppm for 8 months to 25 years (average 4.75 years) (Hollingsworth et al. 1956).

Information regarding hematological effects in animals is scant. No hematologic effects (specific tests not provided) were observed in rats and rabbits exposed to 1,4-DCB vapors at concentrations of 96 or 158 ppm, respectively, dosed for durations of 7 hours/day, 5 days/week for 5–7 months (Hollingsworth et al. 1956). In another intermediate-duration study, F344 rats and BDF_1 mice were chamber-exposed to 25, 55, 120, 270, or 600 ppm of 1,4-DCB for 6 hours/day, 5 days/week for 13 weeks (Aiso et al. 2005a). Hematological changes suggestive of microcytic anemia occurred in the male rats; effects included significantly decreased RBC count and hemoglobin concentration at ≥120 ppm, hematocrit at ≥270 ppm, and MCV and MCH at 600 ppm. The effects were not accompanied by any anemia-associated histopathological changes in hematopoietic tissues (e.g., increased extramedullary hematopoiesis or hemosiderosis in the spleen) and did not occur in the female rats or mice of either sex, leading the investigators to suggest that they were secondary to male rat-specific $\alpha_{2\mu}$-globulin nephropathy-related effects on erythropoietin synthesis in the renal tubules.

A chronic-duration study reported that some changes in blood chemistry and hematologic parameters were seen in rats exposed 5 hours/day, 5 days/week to 1,4-DCB at air concentrations of up to 490–499 ppm for 76 weeks; however, the reported changes showed no consistent trend with dose, sex, or exposure duration that would indicate treatment-related effects (Riley et al. 1980a).

Musculoskeletal Effects.

1,2-Dichlorobenzene. No studies were located regarding musculoskeletal effects in humans following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding musculoskeletal effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,4-DCB.

One study was located that examined the musculoskeletal effects in laboratory animals after inhalation exposure to 1,4-DCB. No gross or histological alterations in skeletal muscle (unspecified parameters) were detected in rats exposed to 1,4-DCB at air concentrations of up to 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks (Riley et al. 1980a).

Hepatic Effects.

1,2-Dichlorobenzene. No studies were located regarding hepatic effects in humans following inhalation exposure to 1,2-DCB.

Increased liver weight and marked central lobular necrosis occurred in rats that were exposed to 1,2-DCB at a concentration of 977 ppm for 0.5 or 1 hour, but not to 539 ppm for 3 hours (Hollingsworth et al. 1958). No changes in absolute liver weight or hepatic histology were reported for rats (20/sex), guinea pigs (8/sex), rabbits (2/sex), or monkeys (2 females) exposed to 93 ppm 1,2-DCB for 7 hours/day, 5 days/week for 6–7 months, or in mice (10 females) similarly exposed to 49 ppm 1,2-DCB (Hollingsworth et al. 1958).

1,3-Dichlorobenzene. No studies were located regarding hepatic effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. Hepatic effects have been reported in humans following long-term exposure to 1,4-DCB via inhalation. A 60-year-old man and his wife who were exposed to moth ball vapor that "saturated" their home for 3–4 months both died of liver failure (acute liver atrophy) within a year of the initial exposure (Cotter 1953). Yellow atrophy and cirrhosis of the liver were reported in a 34-year-old woman who demonstrated 1,4-DCB products in a department store and in a 52-year-old man who used 1,4-DCB occupationally in a fur storage plant for about 2 years (Cotter 1953). Duration of exposure was not estimated for the 34-year-old woman, but was indicated in the report to be >1 year. No estimates of the 1,4-DCB exposure levels (other than the use of the term “saturated”) were provided in any of these reports, nor was it verified that 1,4-DCB exposure was the only factor associated with the observed effects. History of alcohol consumption or prior liver disease factors were not mentioned for any of the cases reported by Cotter (1953). These case studies indicate that the liver is a target organ for 1,4-DCB in humans, but they do not provide quantitative information.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-DCB at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours/day from Gd 6 to 15 produced no adverse clinical or pathological signs in the hepatic tissues of the dams (Hodge et al. 1977). In a similar study, New Zealand White rabbits exposed whole-body to 1,4-DCB 6 hours/day on Gd 6–18 experienced no adverse effects on absolute or relative maternal liver weights at air concentrations up to 800 ppm (Hayes et al. 1985).

An intermediate-duration study was conducted in which F344 rats and BDF_1 mice were chamber-exposed to 0, 25, 55, 120, 270, or 600 ppm of 1,4-DCB for 6 hours/day, 5 days/week for 13 weeks (Aiso et al. 2005a). Hepatic effects in the rats included increases in absolute and relative liver weight (>10%) in males at ≥270 ppm and females at 600 ppm, serum total cholesterol and phospholipid in males at ≥270 ppm and females at 600 ppm, serum albumin in females at ≥270 ppm and males at 600 ppm, total protein in both sexes at 600 ppm, and centrilobular hepatocellular hypertrophy in males at 600 ppm. Hepatic effects in the mice included increases in absolute and relative liver weight (>10%) in males at ≥270 ppm and females at 600 ppm, serum ALT in males at ≥270 ppm and females at 600 ppm, serum AST in males at 600 ppm, serum total cholesterol and total protein in both sexes at 600 ppm, and centrilobular hepatocellular hypertrophy in males at ≥270 ppm and females at 600 ppm. The mouse liver was more responsive to 1,4-DCB than the rat liver as shown by the histological and serum enzyme changes. Hepatocellular hypertrophy occurred at a lower exposure level in the mice (270 ppm compared to 600 ppm in rats); incidences in the 0, 25, 120, 270, and 600 ppm male mice were 0/10, 0/10, 0/10, 0/10; 10/10 and 10/10, respectively. At 600 ppm, the severity of the hepatocellular hypertrophy was classified as moderate in the mice and slight in the rats. Affected hepatocytes in the mice were characterized by cell enlargement, varying nuclear size and shape, and coarse chromatin and inclusion bodies in the nucleus, whereas such nuclear changes were not observed in the hypertrophic hepatocytes of the rats. Additionally, the hepatocellular hypertrophy in the mice was accompanied by single cell necrosis (both sexes, incidence not reported) and focal necrosis (2/10 males) at 600 ppm, as well as the increases in serum ALT at ≥270 ppm and AST at 600 ppm, whereas none of these indicators of hepatocellular damage occurred in the rats.

In a cross-species comparative study, exposure to 1,4-DCB at air concentrations up to 158 ppm, 7 hours/day, 5 days/week for 5–7 months produced no treatment-related effects on liver weight or microscopic appearance in male and female mice; in contrast, various hepatic effects were noted in rats, guinea pigs, and rabbits exposed to 1,4-DCB at various levels and durations of exposure (Hollingsworth et al. 1956). There was considerable variability in the species of animals exposed at each dose, the number of animals exposed, and the total number of exposures. When rats and rabbits inhaled 173–

798 ppm of 1,4-DCB intermittently for 2–12 weeks, several hepatic effects were observed. Relative liver weight was increased in rats exposed to 173 ppm; histopathological examination at this exposure level revealed slight congestion and granular degeneration in female rats. At 798 ppm, liver changes included cloudy swelling and central necrosis in both sexes of rats and rabbits. In the same study, when rats inhaled 158–341 ppm 1,4-DCB intermittently for 5–7 months, male and female rats displayed cloudy swelling and central zone degeneration of the hepatic parenchymal cells in the liver, and increased relative liver weights at 158 ppm. These changes were not seen at a concentration of 96 ppm. In the same study, guinea pigs that were exposed to 341 ppm for a comparable duration or to 798 ppm for 2–4.5 weeks had focal necrosis and slight cirrhosis (in some animals) as well as hepatocyte swelling and degeneration.

In a 2-generation study of the effects of inhalation exposure to 1,4-DCB in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-DCB 6 hours/day for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0–19 and postnatal days 5–27; males were exposed throughout the study. Marked hepatocellular hypertrophy, localized in the centrilobular area, was noted in F_0 and F_1 males and females in the 538 ppm dose group; no such effects were seen in the low- and mid-dose groups. Liver weights were significantly elevated in F_0 males at the 211 and 538 ppm doses and in F_0 females at the 538 ppm dose; liver weights were also significantly elevated in F_1 males and females at the 538 ppm dose (Tyl and Neeper-Bradley 1989). The increased liver weight in F_0 male rats was selected as the critical effect for deriving an intermediate-duration inhalation MRL of 0.2 ppm for 1,4-DCB.

In a long-term inhalation study in rats, exposure to 1,4-DCB at air concentrations of 490–499 ppm 5 hours/day, 5 days/week for 76 weeks resulted in an increase in absolute liver weight throughout the study in males and at weeks 27 and 112 in females (Riley et al. 1980a). This effect was not accompanied by histological alterations or by increased serum transaminase activities. No hepatic effects were noted at 75 ppm. None of the adverse hepatic effects reported at lower concentrations of 1,4-DCB for shorter durations (Hollingsworth et al. 1956), as described above, were identified in the 76-week study.

In another chronic study, groups of 50 male and female F344/DuCrj rats and 50 male and 50 female Crj:BDF_1 mice were exposed to 1,4-DCB in concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Histological examinations showed liver changes only in the high-dose male mice. The incidence of centrilobular

hepatocellular hypertrophy was significantly increased in male mice at 300 ppm, as shown by incidences of 0/49, 0/49, 0/50, and 34/49 in the control to high dose groups.

Renal Effects.

1,2-Dichlorobenzene. Periodic industrial hygiene surveys and medical examinations were conducted in a plant where an unreported number of men were exposed to 1,2-DCB at an average level of 15 ppm (range 1–44 ppm) for an unreported duration (Hollingsworth et al. 1958). No effects on clinical renal indices (blood urea nitrogen, sedimentation rate, or urinalysis) were attributable to exposure.

No changes in absolute kidney weight or kidney histology were reported for rats (20/sex), guinea pigs (8/sex), rabbits (2/sex), or monkeys (2 females) exposed to 93 ppm 1,2-DCB for 7 hours/day, 5 days/week for 6–7 months, or in mice (10 females) similarly exposed to 49 ppm 1,2-DCB (Hollingsworth et al. 1958). Relative kidney weight was not determined. The scope of histological evaluations was not specifically reported; organs that were weighed are inferred to have been histologically examined. Limited urinalysis was performed in the species exposed to 93 ppm; BUN determinations and qualitative tests for sugar, albumin, sediment, and blood showed no abnormalities.

1,3-Dichlorobenzene. No studies were located regarding renal effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding renal effects in humans after inhalation exposure to 1,4-DCB.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-DCB at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours/day from Gd 6 to 15 produced no adverse clinical or pathological signs in the kidney tissues of the dams (Hodge et al. 1977). In a similar study, pregnant New Zealand White rabbits exposed whole-body to 1,4-DCB 6 hours/day on Gd 6–18 experienced no adverse effects with regard to either absolute or relative maternal kidney weights at air concentrations up to 800 ppm (Hayes et al. 1985).

In an intermediate-duration study, F344 rats and BDF_1 mice were chamber-exposed to 25, 55, 120, 270, or 600 ppm of 1,4-DCB for 6 hours/day, 5 days/week for 13 weeks (Aiso et al. 2005a). Histological effects included kidney lesions indicative of $\alpha_{2\mu}$-globulin nephropathy (hyaline droplets, granular casts,

tubular cell necrosis, cytoplasmic basophila, and papillary mineralization) in the male rats at ≥270 ppm. There were no histological changes in the kidneys of the female rats or mice of either sex. Other renal effects included increased relative and/or absolute kidney weights in male rats and male mice at ≥270 ppm and female rats and female mice at 600 ppm, and increased serum BUN in male rats and male mice at 600 ppm.

In rats, mice, and rabbits exposed by inhalation to 1,4-DCB at air concentrations ranging from 96 to 798 ppm, 7 or 8 hours/day, for periods as long as 7 months, no renal effects were noted in mice or rabbits, while both male and female rats experienced increased relative kidney weights at the 173 ppm dose level. In addition, a slight cloudy swelling of the tubular epithelium was noted in female rats exposed to 798 ppm. In the same study, inhalation of 1,4-DCB at 158 or 341 ppm intermittently for 5–7 months by rats caused a slight increase in relative kidney weight in males but not females (Hollingsworth et al. 1956). This effect was not observed in groups of guinea pigs, in one monkey, or in two rabbits under the same experimental conditions (Hollingsworth et al. 1956). The findings in this study are consistent with those reported by Riley et al. (1980a) in a 76-week study in rats, described below.

In a 2-generation study of the effects of inhalation exposure to 1,4-DCB in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-DCB 6 hours/day for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0–19 and postnatal days 5–27; males were exposed throughout the study. An increased incidence of nephrosis was seen in F_0 males of all dose groups and in F_1 males of the 211 and 538 ppm dose groups; lesions consisted of hyaline droplets, tubular protein nephrosis, granular cast formation, and interstitial nephritis. No renal lesions were noted in F_0 or F_1 females. Kidney weights were significantly elevated in F_0 males at all doses and in F_1 males at the 538 ppm dose. In females, kidney weights were significantly elevated in the F_0 generation at the 538 ppm dose, but were not elevated in the F_1 generation (Tyl and Neeper-Bradley 1989).

In a chronic-duration inhalation study in Wistar rats, exposure to 1,4-DCB at air concentrations of 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks resulted in an increase in absolute kidney weight in males throughout the study and in females at weeks 27 and 112 weeks. Exposure to 75 ppm 1,4-DCB had no effect on kidney weight, and neither exposure level caused histopathological alterations in the kidneys (Riley et al. 1980a). In another chronic study, groups of 50 male and female F344/DuCrj rats and 50 male and 50 female Crj:BDF_1 mice were exposed to 1,4-DCB in concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Histological examinations showed kidney changes only in male rats at 300 ppm, where incidences of

mineralization of the renal papilla and hyperplasia of the urothelium were significantly increased. In general, the renal effects observed in inhalation studies of 1,4-DCB are mild in contrast with the severe renal effects observed in oral studies as described in Section 3.2.2.2.

Endocrine Effects.

1,2-Dichlorobenzene. No studies were located regarding endocrine effects in humans or animals following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding endocrine effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,4-DCB.

The only information regarding endocrine effects in animals after inhalation exposure to 1,4-DCB is from a chronic-duration study in rats. In that study (Riley et al. 1980a), no gross or histopathological effects were observed in the adrenal, thyroid, or pituitary glands of male or female rats exposed to 1,4-DCB at air concentrations up to 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks. No further information regarding endocrine effects was located.

Dermal Effects.

1,2-Dichlorobenzene. No studies were located regarding dermal effects in humans or animals following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding dermal effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. Dermal effects resulting from 1,4-DCB exposure were reported in a 69-year-old man who had been exposed for approximately 3 weeks to 1,4-DCB used in his home, including on a chair on which he had been sitting. He gradually developed petechiae (small red spots), purpura (purple or brownish-red spots), and swelling of his hands and feet. His sensitivity to 1,4-DCB was established by an

indirect basophil degranulation test that showed a strongly positive reaction (degenerative changes in 62% of his basophils when tested with 1,4-DCB, compared with a 6% reaction of normal serum with 1,4-DCB) (Nalbandian and Pearce 1965). The authors suggested that these effects were probably immunologically mediated. In a study of 58 men occupationally exposed to up to 725 ppm 1,4-DCB, 8 hours/day, 5 days/week continually or intermittently for 8 months to 25 years (average: 4.75 years), medical examinations revealed no evidence of dermatological effects (Hollingsworth et al. 1956).

No studies were located regarding dermal effects in animals after inhalation exposure to 1,4-DCB.

Ocular Effects.

1,2-Dichlorobenzene. Periodic industrial hygiene surveys and medical examinations were conducted in a plant where an unreported number of men were exposed to 1,2-DCB at an average level of 15 ppm (range 1–44 ppm) for an unreported duration (Hollingsworth et al. 1958). No eye or nasal irritation was attributable to exposure. Additionally, Hollingsworth et al. (1958) noted that his researchers detected 1,2-DCB odor at a concentration of 50 ppm without eye or nasal irritation during repeated vapor inhalation experiments on animals. An earlier source (Elkins 1950) referenced by Hollingsworth (1958) reported that occupational exposure to 100 ppm of 1,2-DCB caused irritation of the eyes and respiratory passages.

1,3-Dichlorobenzene. No studies were located regarding ocular effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. In a report on 58 men who had worked for 8 months to 25 years (average exposure 4.75 years) in a plant that used 1,4-DCB, painful irritation of the nose and eyes were reported at levels ranging from 80 to 160 ppm (Hollingsworth et al. 1956). At levels >160 ppm, the air was considered unbreathable by unacclimated persons. Neither cataracts nor any other lens changes were found upon examination of their eyes.

There is no clear, quantitative evidence of ocular effects resulting from inhalation exposure to 1,4-DCB in animal studies. Ocular effects, described as reversible, nonspecific eye ground changes (changes in the fundus or back of the eye), were seen in two rabbits exposed to 1,4-DCB at 798 ppm, 8 hours/day, 5 days/week for 12 weeks (Hollingsworth et al. 1956). In the same study, no lens changes were observed in rats or guinea pigs exposed to 798 ppm 1,4-DCB, but eye irritation was reported in the three species

tested. Ocular effects occurring during and/or after exposure to chemicals in air are likely to be due to direct contact of the chemical with the eye.

A chronic-duration inhalation study in male and female Wistar rats reported no histopathological alterations in the eyes of rats exposed to 1,4-DCB at air concentrations up to 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks (Riley et al. 1980a). No further data were located.

Body Weight Effects.

1,2-Dichlorobenzene. Groups of male and female albino rats (20/sex) were exposed to 0, 49, or 93 ppm (0, 290, or 560 mg/m^3, respectively) of 1,2-DCB (99% pure) vapor for 7 hours/day, 5 days/week for 6–7 months (Hollingsworth et al. 1958). No compound related effects were found at 49 ppm. Effects observed at 93 ppm consisted of statistically significant ($p \leq 0.05$) decreased final body weight in the males (8.9% lower than controls). There were no body weight changes in guinea pigs (8/sex), rabbits (2/sex), or monkeys (2 females) similarly exposed to 93 ppm 1,2-DCB, or in mice (10 females) similarly exposed to 49 ppm 1,2-DCB (Hollingsworth et al. 1958).

1,3-Dichlorobenzene. No studies were located regarding body weight effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. A 60-year-old man who was exposed to vapors of 1,4-DCB in his home for 3–4 months was reported to have lost approximately 50 pounds in body weight in 3 months (Cotter 1953). His wife, who received similar exposure, also lost weight. A third case reported by the same author (Cotter 1953) is that of a 52-year-old man who was exposed to 1,4-DCB by using the chemical for preserving raw furs. On examination, this individual was described as being emaciated. Information regarding food consumption was not available in any of these cases. In the case of the 60-year-old man, persistent diarrhea may have contributed to the weight loss.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-DCB at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours/day from Gd 6 to 15 had no effect on maternal body weight gain (Hodge et al. 1977).

Body weight data are available for various animal species after exposure to 1,4-DCB 7–8 hours/day, 5 days/week, for periods ranging from 2 weeks to 6 months (Hollingsworth et al. 1956). Rats, rabbits,

and guinea pigs experienced weight loss when exposed to 798 ppm, 8 hours/day, 5 days/week. Rats exposed to up to 341 ppm 1,4-DCB for 5–7 months grew at a rate similar to that of unexposed controls. Similar results were obtained in rabbits exposed to 173 ppm for 16 days or to 158 ppm for about 200 days. Slight growth depression was observed in male and female guinea pigs exposed to 158 ppm 1,4-DCB for 157 days, but only males showed a slight delay in growth when the exposure level was 341 ppm for 6 months. In male and female mice and in one female monkey, there were no effects on body weight after exposure to 1,4-DCB at air concentrations up to 158 ppm for as long as 7.1 months. In another intermediate-duration study, there were no effects on body weight gain in F344 rats and BDF_1 mice that were exposed to 25, 55, 120, 270, or 600 ppm of 1,4-DCB for 6 hours/day, 5 days/week for 13 weeks (Aiso et al. 2005a).

In a 2-generation study of the effects of inhalation exposure to 1,4-DCB in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-DCB 6 hours/day for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0–19 and postnatal days 5–27; males were exposed throughout the study. Male F_0 body weight and body weight gain were significantly reduced in the 538 ppm group. Body weight gain was also significantly reduced in the 211 ppm group; however, the effect was seen at fewer observation periods. Female F_0 body weights were equivalent across all treatment groups during the entire prebreeding period. The F_1 generation males and females exposed to 538 ppm 1,4-DCB had lower body weights than did controls; however, these decreases were accompanied by decreased food consumption (Tyl and Neeper-Bradley 1989).

A chronic-duration inhalation study in male and female Wistar rats found that body weight was not significantly altered after exposure to 1,4-DCB at air concentrations up to 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks (Riley et al. 1980a).

Other Systemic Effects.

1,2-Dichlorobenzene. No studies were located regarding other systemic effects in humans or animals following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding other systemic effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding other effects in humans following inhalation exposure to 1,4-DCB. Ascites, esophageal varices, hemorrhoids, and tarry stools are all secondary effects of subacute, yellow atrophy and cirrhosis of the liver (Cotter 1953).

A chronic-duration inhalation study in male and female Wistar rats found that food and water consumption was not significantly altered after exposure to 1,4-DCB at air concentrations up to 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks (Riley et al. 1980a).

In a 2-generation study of the effects of inhalation exposure to 1,4-DCB in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-DCB 6 hours daily for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0–19 and postnatal days 5–27; males were exposed throughout the study. Exposure of the F_0 and F_1 generations to 538 ppm 1,4-DCB resulted in clinical signs of toxicity such as decreased grooming, unkempt appearance, decreased food consumption, and dehydration (Tyl and Neeper-Bradley 1989).

3.2.1.3 Immunological and Lymphoreticular Effects

1,2-Dichlorobenzene. No studies were located regarding immunological effects in humans following inhalation exposure to 1,2-DCB.

No changes in absolute spleen weight or spleen histology were reported for rats (20/sex) or guinea pigs (8/sex) that were exposed to 93 ppm 1,2-DCB for 7 hours/day, 5 days/week for 6–7 months (Hollingsworth et al. 1958). Relative spleen weight was not determined. The scope of histological evaluations was not specifically reported; organs that were weighed appear to have been examined.

1,3-Dichlorobenzene. No studies were located regarding immunological effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. As mentioned in Section 3.2.1.2, dermal effects observed in a 69-year-old man who had been exposed to 1,4-DCB in his home for approximately 3 weeks (Nalbandian and Pearce 1965) may have been mediated by immunological mechanisms. In addition to petechiae, purpura, and swelling of his hands and feet, his serum showed a strong positive reaction to 1,4-DCB in an indirect basophil degranulation test. The authors stated that, to their knowledge, this was the first reported case of allergic (anaphylactoid) purpura induced by exposure to 1,4-DCB. Enlargement of the spleen was reported in a

woman who had been exposed to 1,4-DCB in her home for 3–4 months and in a man who used 1,4-DCB to preserve raw furs (Cotter 1953). This, however, was most likely a secondary response to hematological disturbances rather than an immunological effect.

A slight decrease in relative spleen weight was observed in male guinea pigs exposed to 1,4-DCB at an air concentration of 173 ppm, 7 hours/day, 5 days/week for 16 days (Hollingsworth et al. 1956); no effect was seen in rats under the same experimental conditions. In a chronic-duration inhalation study, groups of male and female Wistar rats exposed to 1,4-DCB 5 hours/day, 5 days/week for 76 weeks exhibited no gross or histopathological alterations in the cervical, thoracic, and mesenteric lymph nodes; spleen; or thymus at air concentrations up to 500 ppm (Riley et al. 1980a). No other immunological end points were evaluated.

No effects were found in an immunotoxicity study in which groups of 10 male SPF Hartley guinea pigs were exposed to 1,4-DCB by inhalation in concentrations of 0, 2, or 50 ppm for 12 weeks (schedule not specified) (Suzuki et al. 1991). The animals were sensitized with ovalbumin after 4 and 8 weeks of exposure to evaluate effects on antibody production. Determinations of serum IgE titers (passive cutaneous anaphylaxis test) and serum IgG and IgM titers (enzyme-linked immunosorbent assay) against ovalbumin, performed 1 and 2 weeks after the first sensitization and 1, 2, and 4 weeks after the second sensitization, showed no significant differences between the exposed and control groups. The passive cutaneous anaphylaxis test was also conducted with antiserum from the 50 ppm exposure group (collected 1 and 2 weeks after the first sensitization and 1, 2, and 4 weeks after the second sensitization) to determine if IgE antibodies were produced against 1,4-DCB; no antibodies against the compound were detected. Active systemic anaphylaxis was also evaluated in the 0 and 50 ppm exposure groups. An antigen mixture of 1,4-DCB and guinea pig serum albumin did not cause an anaphylactic reaction when intravenously injected in the animals 14 days after the last exposure. This study was reported in the Japanese literature; relevant information was obtained from the English abstract and data tables.

3.2.1.4 Neurological Effects

1,2-Dichlorobenzene. No studies were located regarding neurological effects in humans or animals following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding neurological effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. Information regarding neurological effects in humans exposed to 1,4-DCB via inhalation is limited to several case reports. A 60-year-old man whose home had been saturated with 1,4-DCB moth ball vapor for 3 or 4 months complained of persistent headache, numbness, clumsiness, and a burning sensation in his legs (consistent with peripheral nerve damage); he also showed slurred speech (Cotter 1953). In a more recent case study, a 25-year-old woman was exposed to high concentrations of 1,4-DCB from her bedroom, bedding, and clothing. She had used this compound liberally as an insect repellant for 6 years. The subject sought medical assistance because of severe ataxia, speech difficulties, and moderate weakness of her limbs. Brainstem auditory-evoked potentials (BAEPs) showed marked delays of specific brainwave patterns. Her symptoms gradually improved over the next 6 months after cessation of exposure and the BAEPs examined 8 months later had returned to normal. This study suggests that there may be measurable but reversible neurological effects associated with human inhalation exposure to 1,4-DCB (Miyai et al. 1988). The level of 1,4-DCB exposure was neither known nor estimated in either of the human case studies. In addition, there is no certainty that exposure to 1,4-DCB was the only factor associated with the toxic effects reported.

Neurological signs including marked tremors, weakness, and loss of consciousness were observed in rats, rabbits, and guinea pigs exposed to 798 ppm 1,4-DCB 8 hours/day, 5 days/week (Hollingsworth et al. 1956). In a chronic-duration study in rats, exposure to up to 500 ppm 1,4-DCB 5 hours/day, 5 days/week for 76 weeks did not cause gross or histological alterations in the brain, sciatic nerve, or spinal cord, but absolute brain weight was slightly decreased at the termination of the study (Riley et al. 1980a). Adult rats exposed 6 hours/day for 10 weeks to 538 ppm 1,4-DCB during a 2-generation study displayed symptoms associated with compound neurotoxicity, including tremors, ataxia, and hyperactivity (Tyl and Neeper-Bradley 1989). The animals also decreased their grooming behavior and developed an unkempt appearance. At sacrifice, the relative brain weights of the males, but not the females, were significantly increased compared to the controls.

3.2.1.5 Reproductive Effects

1,2-Dichlorobenzene. No studies were located regarding reproductive effects in humans or animals following inhalation exposure to 1,2-DCB.

A 2-generation inhalation reproduction study was conducted in which groups of Charles River CD (Sprague-Dawley derived) rats (30/sex/generation) were exposed to 1,2-DCB at levels of 0, 50, 150, or

394 ppm (Bio/dynamics 1989). F_0 adults were exposed for 6 hours/day, 7 days/week for a 10-week premating period and during mating. Following mating, F_0 males were exposed 6 hours/day, 7 days/week until sacrifice at 3–4 weeks postmating. Bred F_0 females were exposed for 6 hours/day on gestation days 0–19 and lactation days 5–28, then sacrificed postweaning. F_1 pups (29 days old) received similar exposures throughout an 11-week premating period, mating, gestation, and lactation. There were no exposure-related effects on reproductive performance or fertility indices in either generation.

No changes in absolute testicular weight or testicular histology were reported for male rats or guinea pigs that were exposed to 93 ppm 1,2-DCB for 7 hours/day, 5 days/week for 6–7 months (Hollingsworth et al. 1958). Relative testicular weight was not determined. The scope of histological evaluations in this study was not specifically reported; organs that were weighed also appear to have been examined.

1,3-Dichlorobenzene. No studies were located regarding reproductive effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding reproductive effects in humans after inhalation exposure to 1,4-DCB.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-DCB at air concentrations up to 508.4 ppm, 6 hours/day from Gd 6 to 15 did not adversely affect the number of implantations, resorptions, viable fetuses, corpora lutea, or sex ratios (Hodge et al. 1977). A similar study in inseminated New Zealand White rabbits exposed whole-body to 1,4-DCB at air concentrations of 100, 300, or 800 ppm, 6 hours/day on Gd 6–18 found no differences between treated and control groups in the mean number of corpora lutea per dam, the mean number of implantation sites per dam, the mean number of resorptions per litter, or the number of totally resorbed litters. At 300 ppm, there was a significant increase ($p \leq 0.05$) in the percentage of resorbed implantations per litter and in the number of litters with resorptions; however, the results at 800 ppm were comparable to controls, and the percentage of litters with resorptions reported in the 300 ppm group was within the range reported for historical controls, suggesting this effect was not chemical- or dose-related (Hayes et al. 1985).

Exposure of rats and guinea pigs to 1,4-DCB at an air concentration of 173 ppm, 7 hours/day, 5 days/week for 2 weeks did not significantly alter relative testis weight. The same results were obtained after intermittently exposing rats and guinea pigs to 1,4-DCB at air concentrations up to 158 ppm for 5–7 months (Hollingsworth et al. 1956). There were no treatment-related effects on the reproductive organs

of male or female Wistar rats exposed to 1,4-DCB at concentrations up to 490–499 ppm, 5 hours/day, 5 days/week for 76 weeks (Riley et al. 1980a). The evaluation of reproductive end points included organ weights and histopathology.

In another chronic inhalation study, groups of 50 male and female F344/DuCrj rats and 50 male and 50 female Crj:BDF_1 mice were exposed to 1,4-DCB in concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Histological examinations included reproductive system tissues in both sexes (testis, epididymis, seminal vesicle, prostate, ovary, uterus, vagina, and mammary gland), but there were no exposure-related adverse findings in either species or sex (Aiso 2006).

The effects of 1,4-DCB vapors on the reproductive performance of Sprague-Dawley rats was assessed in a 2-generation study in which animals of both sexes were exposed before and during mating (Tyl and Neeper-Bradley 1989). The females were then exposed on Gd 0–19 and postnatal days 5–27. Effects on body weight, liver and kidney weight, and hepatocellular hypertrophy were found in the adult rats at exposure concentrations of 211 and 538 ppm and were indicative of toxicity to the breeding animals. These effects did not occur with the 66.3 ppm exposure concentration. Both generations of offspring exposed to the 538 ppm concentration had lower body weights than the controls at lactation day 4; average litter size and survival rates were decreased. When selected animals from the first filial generation were allowed to recover from the 1,4-DCB exposure for a 5-week period, body weights of the 538 ppm exposure group remained lower than those for the controls. The authors concluded that parental toxicity was the cause of the increased risk to offspring rather than inherent effects of 1,4-DCB on reproductive processes. In addition, no reduction in reproductive performance (as measured by the percentage of males successfully impregnating females) was observed in an inhalation study in which male mice were exposed to 1,4-DCB at 75–450 ppm for 6 hours/day for 5 days before being mated with virgin females (Anderson and Hodge 1976). These data are consistent with the data from the males used in the 2-generation study discussed above.

3.2.1.6 Developmental Effects

1,2-Dichlorobenzene. No studies were located regarding developmental effects in humans or animals following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding developmental effects in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding developmental effects in humans after inhalation exposure to 1,4-DCB.

Exposure of pregnant Alderley-Park rats to 1,4-DCB via inhalation at levels up to 508 ppm for 6 hours/day on Gd 6–15 did not result in developmental effects in the offspring (Hodge et al. 1977). End points examined included the number of viable fetuses, fetal weight, litter weight, sex ratio, external abnormalities, and skeletal and visceral abnormalities.

In a 2-generation study of the effects of inhalation exposure to 1,4-DCB in Sprague-Dawley rats, males and females that were exposed to 0, 66.3, 211, or 538 ppm 1,4-DCB 6 hours daily for 10 weeks prior to mating were assessed. The females were also exposed during mating, and on Gd 0–19 and postnatal days 5–27; males were exposed throughout the study. F_1 and F_2 pup body weights in the 538 ppm group were significantly reduced from postnatal day 0 to 28. The number of F_1 and F_2 pups that died during the perinatal period was significantly elevated in the 538 ppm group (Tyl and Neeper-Bradley 1989).

The developmental effects of 1,4-DCB have been evaluated in New Zealand White rabbits (Hayes et al. 1985). Pregnant rabbits were exposed to 1,4-DCB by inhalation at 800 ppm for 6 hours/day on Gd 6–18. At 300 ppm, there was a significant increase in the number of litters with resorptions and the percentages of resorbed implantations per litter; however, this effect was not seen at 800 ppm and was thus probably not treatment-related. An increased incidence of retroesophageal right subclavian artery present in the offspring was noted; it was not considered to constitute a teratogenic response to exposure to 1,4-DCB, but was considered only a minor variation.

3.2.1.7 Cancer

1,2-Dichlorobenzene. No studies were located regarding cancer in humans or animals following inhalation exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding cancer in humans or animals following inhalation exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding cancer in humans after inhalation exposure to 1,4-DCB.

No evidence of carcinogenicity was observed in a long-term inhalation study in rats that were exposed to 1,4-DCB at 75 or 500 ppm intermittently for 76 weeks (Riley et al. 1980a). The reported lack of extensive organ toxicity in this study (compared with results seen in oral studies described in Section 3.2.2.2) strongly suggests that a maximum tolerated dose (MTD) was not achieved. In addition, a less-than-lifetime dosing regimen was used. The experimental design limitations preclude reliable evaluation of potential inhalation carcinogenicity based on this study.

The carcinogenicity of 1,4-DCB was more recently evaluated in groups of 50 male and female F344/DuCrj rats, and 50 male and 50 female Crj:BDF_1 mice, following exposure to concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Comprehensive histological evaluations (including nasal cavity, trachea, and lungs) showed no compound-related neoplastic changes in rats, although incidences of liver and lung tumors were elevated in mice. The liver tumors were induced in mice of both sexes, generally increased only at 300 ppm, and were comprised of several tumor types. Liver tumors reported to be significantly increased ($p \leq 0.05$, Fisher's Exact test) in male mice were hepatocellular carcinoma (12/49, 17/49, 16/50, 38/49; $p \leq 0.01$ at high dose), hepatoblastoma (0/49, 2/49, 0/50, 8/49; $p \leq 0.01$ at high dose) and hepatic histiocytic sarcoma (0/49, 3/49, 1/50, 6/49; $p \leq 0.05$ at high dose). Liver tumors reported to be significantly increased in female mice were hepatocellular carcinoma (2/50, 4/50, 2/49, 41/50; $p \leq 0.01$ at high dose), hepatocellular adenoma (2/50, 10/50, 6/49, 20/50; $p \leq 0.05$ at low and high doses), hepatocellular carcinoma or adenoma (4/50, 13/50, 7/49, 45/50; $p \leq 0.05$ at low and high doses), and hepatoblastoma (0/50, 0/50, 0/49, 6/50; $p \leq 0.05$ at high dose). Although the hepatocellular adenomas were increased in female mice at 20 and 300 ppm, the relevance of the increase at 20 ppm is unclear given the lack of significant change at 75 ppm. Lung bronchoalveolar adenoma and carcinoma were significantly increased in female mice (1/50, 4/50, 2/49, 7/50; $p \leq 0.05$ at high dose). Except for hepatoblastoma, all of the aforementioned liver and lung tumor incidences were reported to have a significant positive linear trend by the Peto test and/or Cochran-Armitage test.

3.2.2 Oral Exposure

Most of the data described in this section were derived from laboratory studies in which 1,2-, 1,3-, and 1,4-DCB were administered to test animals via gavage. In addition, two human case studies of 1,4-DCB

consumption are described. Case studies are not generally scientifically equivalent to well-conducted epidemiologic studies or laboratory experiments and should be viewed only as providing contributory evidence that 1,4-DCB may have caused the reported effects. The available case studies do not provide unequivocal proof that 1,4-DCB is solely responsible for the reported toxicological effects in humans. The highest NOAEL and all reliable LOAEL values after oral exposure to 1,2-, 1,3-, and 1,4-DCB are recorded in Tables 3-3, 3-4, and 3-5, respectively, and plotted in Figures 3-3, 3-4, and 3-5, respectively.

3.2.2.1 Death

1,2-Dichlorobenzene. No studies were located regarding death in humans after oral exposure to 1,2-DCB.

Single-dose LD_{50} values of 500 and 1,516 mg/kg have been reported for 1,2-DCB in rats administered the compound in oil by gavage (Ben-Dyke et al. 1970; Monsanto 1989). Rats that were gavaged with a 25% solution of 1,2-DCB in peanut oil at a dose of 675 mg/kg/day for 3 days were considered unlikely to survive further exposures (DuPont 1982). Guinea pigs that were treated with a single gavage dose of 1,2-DCB as a 50% solution in olive oil had no deaths at 800 mg/kg and 100% mortality at 2,000 mg/kg (Hollingsworth et al. 1958).

Rats that were administered 1,2-DCB in oil by gavage for 14 consecutive days and observed until day 20 experienced 100% mortality at 1,000 mg/kg/day and no deaths at 500 mg/kg/day and lower doses (NTP 1985). Mice that were similarly treated with 1,2-DCB for 14 days had 80% mortality in both sexes at 250 mg/kg/day (lowest tested dose) and 80–100% mortality at ≥500 mg/kg/day (NTP 1985). The reliability of the 14-day findings is uncertain because there were no clear effects of gavage exposure to 1,2-DCB in oil on survival in rats or mice exposed to ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), rats exposed to 400 mg/kg/day on 7 days/week for 90 days (Robinson et al. 1991), or rats or mice exposed to ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985). Information in the longer-term NTP (1985) studies suggests that gavage error might have contributed to some of the deaths in the 14-day studies.

1,3-Dichlorobenzene. No studies were located regarding death in humans after oral exposure to 1,3-DCB.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Death									
1	Rat (NS)	once (NS)				500	(LD50)	Ben-Dyke et al. 1970 1,2-dichlorobenzene	
2	Rat (NS)	once (GO)				1500	(lowest lethal dose)	DuPont 1982 1,2-dichlorobenzene	
3	Rat (NS)	3 d 1 x/d (GO)				675	(unlikely to survive further exposure)	DuPont 1982 1,2-dichlorobenzene	
4	Rat (NS)	once (G)				1516	(LD50)	Monsanto 1989 1,2-dichlorobenzene	
5	Rat (Fischer- 344)	14 d 7 d/wk 1 x/d (GO)				1000	(100% mortality)	NTP 1985 1,2-dichlorobenzene	
6	Mouse (B6C3F1)	14 d 7 d/wk 1 x/d (GO)				250	(80% mortality)	NTP 1985 1,2-dichlorobenzene	
7	Gn Pig (NS)	once (GO)				2000	(100% mortality)	Hollingsworth et al. 1958 1,2-dichlorobenzene	
Systemic									
8	Rat (NS)	once (GO)	Hepatic			1500	(central necrosis)	DuPont 1982 1,2-dichlorobenzene	
			Renal			1500	(albuminous fluid and casts in tubules)		

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Rat (NS)	3 d 1 x/d (GO)	Bd Wt			675 (10% body weight loss)	DuPont 1982 1,2-dichlorobenzene	
10	Rat (Fischer- 344)	14 d 7 d/wk 1 x/d (GO)	Hepatic	1000			NTP 1985 1,2-dichlorobenzene	
			Bd Wt	500[b] M 1000 F	1000 M (12% reduced body weight gain)			

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
11	Rat (Sprague-Dawley)	10 d 7 d/wk 1 x/d (GO)	Resp	300 M			Robinson et al. 1991 1,2-dichlorobenzene	
			Cardio	300				
			Gastro	300 M				
			Hemato	300 M				
			Musc/skel	300 M				
			Hepatic	150 M 75[c] F	300 M (slight necrosis, increased serum ALT) 150[b] F (increased liver weight)			
			Renal	300 M				
			Endocr	300 M				
			Dermal	300				
			Bd Wt	150[b] M 300 F	300 M (10.9% reduced body weight gain)			
12	Mouse (B6C3F1)	14 d 7 d/wk 1 x/d (GO)	Hepatic		250 (hepatocellular degeneration)		NTP 1985 1,2-dichlorobenzene	

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
13	Mouse (B6C3F1)	14 d 7 d/wk 1 x/d (GO)	Hepatic		500 (hepatocellular necrosis and degeneration)		NTP 1985 1,2-dichlorobenzene	
			Bd Wt	500				
Immuno/ Lymphoret								
14	Rat (Sprague-Dawley)	10 d 7 d/wk 1 x/d (GO)		300			Robinson et al. 1991 1,2-dichlorobenzene	
Developmental								
15	Rat (Sprague-Dawley)	10 d Gd 6-15 (G)		200 F			Ruddick et al. 1983 1,2-dichlorobenzene	
INTERMEDIATE EXPOSURE								
Systemic								
16	Rat (NS)	192 d 5 d/wk	Hemato	376 F			Hollingsworth et al. 1958 1,2-dichlorobenzene	
			Hepatic		376 F (slight to moderate cloudy swelling)			
			Renal	376 F				
			Bd Wt	376 F				

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)	Resp	500			NTP 1985 1,2-dichlorobenzene	
			Cardio	500				
			Gastro	500				
			Hemato	500				
			Musc/skel	500				
			Hepatic	60[d]	125 (increased liver weight)			
			Renal	250[b] M 500 F	500 M (renal tubular degeneration)			
			Endocr	500				
			Dermal	500				
			Ocular	500				
			Bd Wt	250[b] M 500 F	500 M			
18	Rat (albino)	15 d 1 x/d (G)	Hepatic			455 M (necrosis and fatty changes, porphyria)	Rimington and Ziegler 1963 1,2-dichlorobenzene	

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (Sprague-Dawley)	90 d 7 d/wk 1 x/d (GO)	Resp	400 M			Robinson et al. 1991 1,2-dichlorobenzene	
			Cardio	400				
			Hepatic		400 (centrilobular degeneration, single cell necrosis)			
			Renal	400				
			Endocr	400 M				
			Bd Wt		400 M (12.8% decreased body weight gain)			

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
20	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)	Resp	500			NTP 1985 1,2-dichlorobenzene	
			Cardio	250	500 (mineralization of myocardial fibers)			
			Gastro	500				
			Hemato	500				
			Musc/skel	250	500 (mineralization of myocardial and skeletal muscle fibers)			
			Hepatic	125[b] M 250 F	250[b] M (single cell necrosis, hepatocellular degeneration) 500 F			
			Renal	500				
			Endocr	500				
			Dermal	500				
			Ocular	500				
			Bd Wt	500	500 (11-19% reduced body weight gain)			

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
21	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)		250 M	500 M (lymphoid depletion in thymus)		NTP 1985 1,2-dichlorobenzene	
22	Rat (Sprague-Dawley)	90 d 7 d/wk 1 x/d (GO)		400			Robinson et al. 1991 1,2-dichlorobenzene	
23	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)		500			NTP 1985 1,2-dichlorobenzene	
Neurological								
24	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)		500			NTP 1985 1,2-dichlorobenzene	
25	Rat (albino)	15 d 1 x/d (G)				455 M (ataxia, clonic contractions)	Rimington and Ziegler 1963 1,2-dichlorobenzene	
26	Rat (Sprague-Dawley)	90 d 7 d/wk 1 x/d (GO)		400			Robinson et al. 1991 1,2-dichlorobenzene	
27	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)		500			NTP 1985 1,2-dichlorobenzene	

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
28	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)		500			NTP 1985 1,2-dichlorobenzene	
29	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)		500			NTP 1985 1,2-dichlorobenzene	
CHRONIC EXPOSURE								
Systemic								
30	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)	Resp	120			NTP 1985 1,2-dichlorobenzene	
			Cardio	120				
			Gastro	120				
			Musc/skel	120				
			Hepatic	120				
			Renal	120				
			Endocr	120				
			Dermal	120				
			Ocular	120				
			Bd Wt	120				

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
31	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)	Resp	120			NTP 1985 1,2-dichlorobenzene	
			Cardio	120				
			Gastro	120				
			Musc/skel	120				
			Hepatic	120				
			Renal	60[e]	120 (renal tubular regeneration)			
			Endocr	120				
			Dermal	120				
			Ocular	120				
			Bd Wt	120				
Immuno/ Lymphoret								
32	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)		120			NTP 1985 1,2-dichlorobenzene	
33	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)		120			NTP 1985 1,2-dichlorobenzene	

Table 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
34	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)		120			NTP 1985 1,2-dichlorobenzene	
35	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)		120			NTP 1985 1,2-dichlorobenzene	
Reproductive								
36	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)		120			NTP 1985 1,2-dichlorobenzene	

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

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Study result used to derive an acute-duration oral Minimal Risk Level (MRL) of 0.7 mg/kg/day for 1,2-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on liver weight data to select a point of departure, which was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

d Study result used to derive an intermediate-duration oral Minimal Risk Level (MRL) of 0.6 mg/kg/day for 1,2-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on liver weight data to select a point of departure, which was adjusted for daily exposure, then divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

e Study result used to derive a chronic-duration oral Minimal Risk Level (MRL) of 0.3 mg/kg/day for 1,2-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on incidences of kidney lesions to select a point of departure, which was adjusted for daily exposure, then divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ALT = alamine aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; x = time(s)

Figure 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral

Acute (≤14 days)

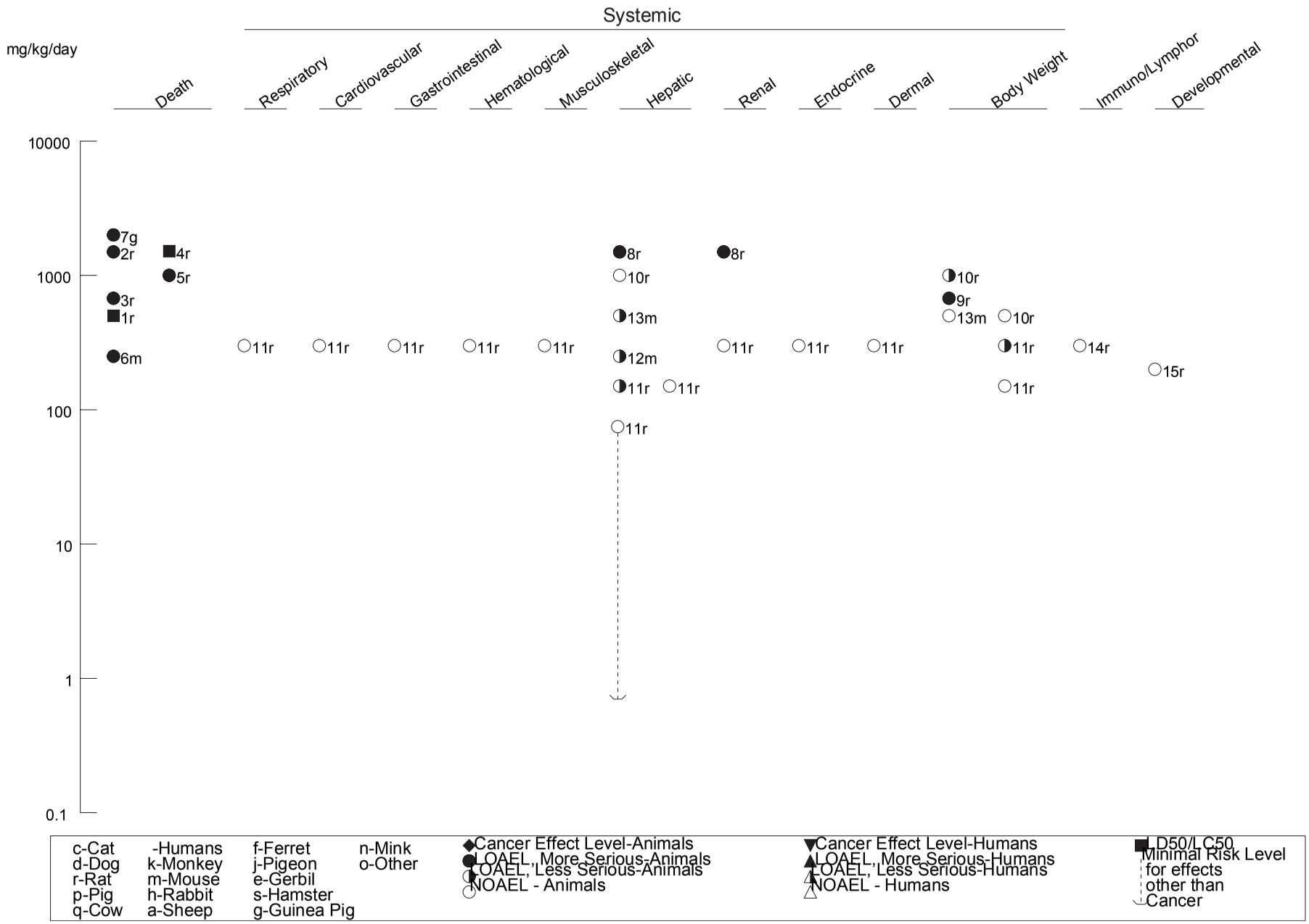


Figure 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral *(Continued)*

Intermediate (15-364 days)

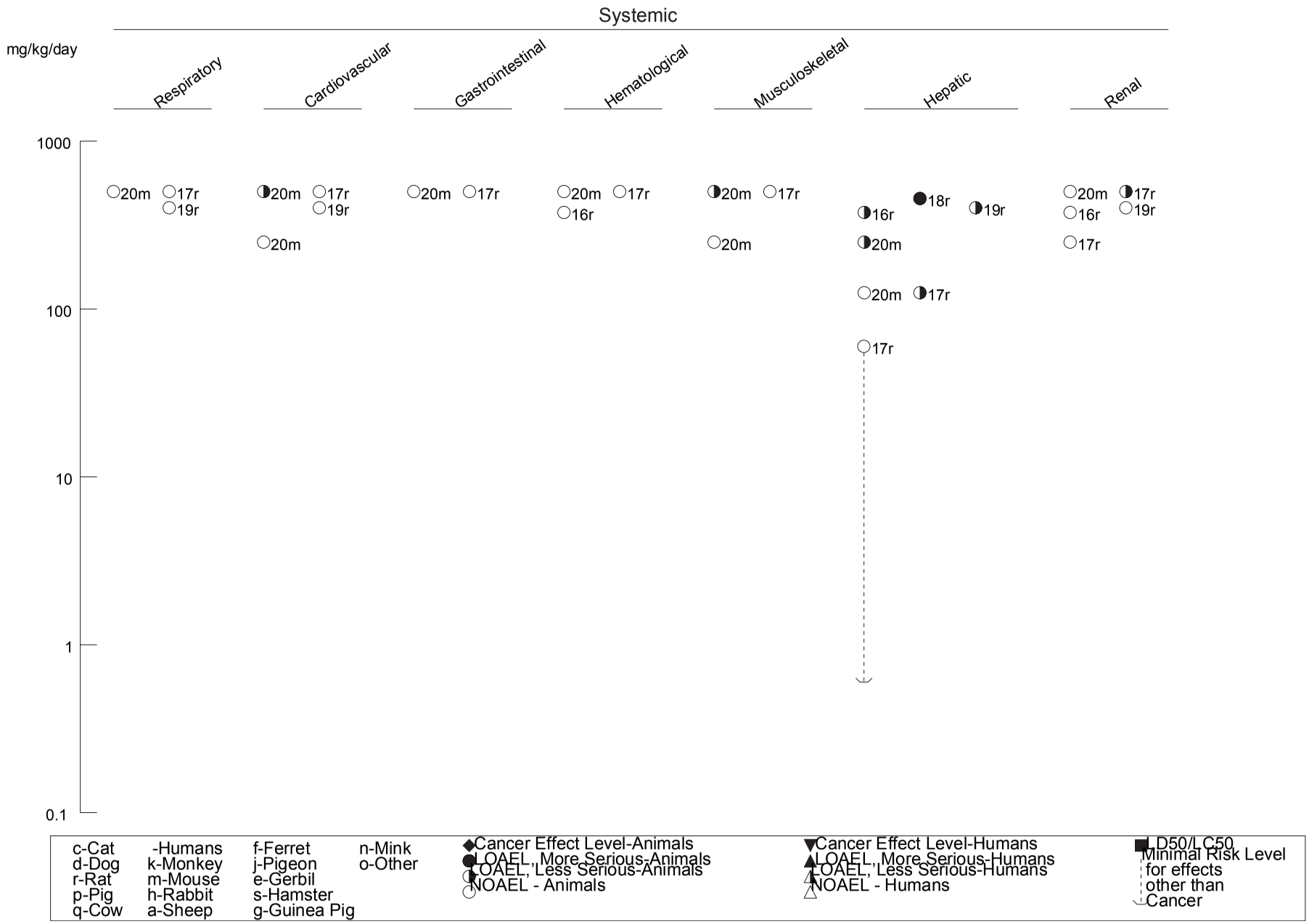


Figure 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral *(Continued)*

Intermediate (15-364 days)

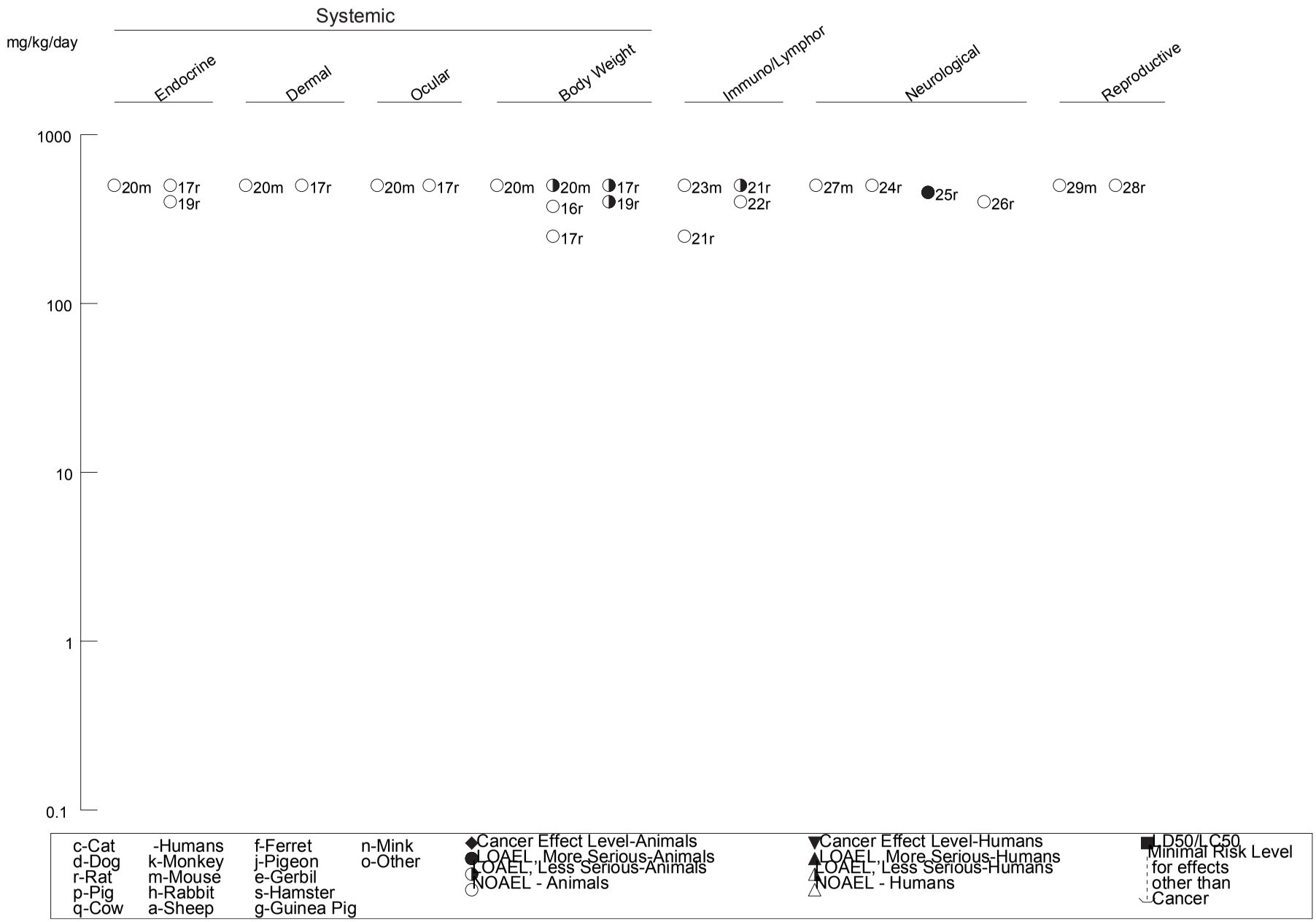


Figure 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral *(Continued)*

Chronic (≥365 days)

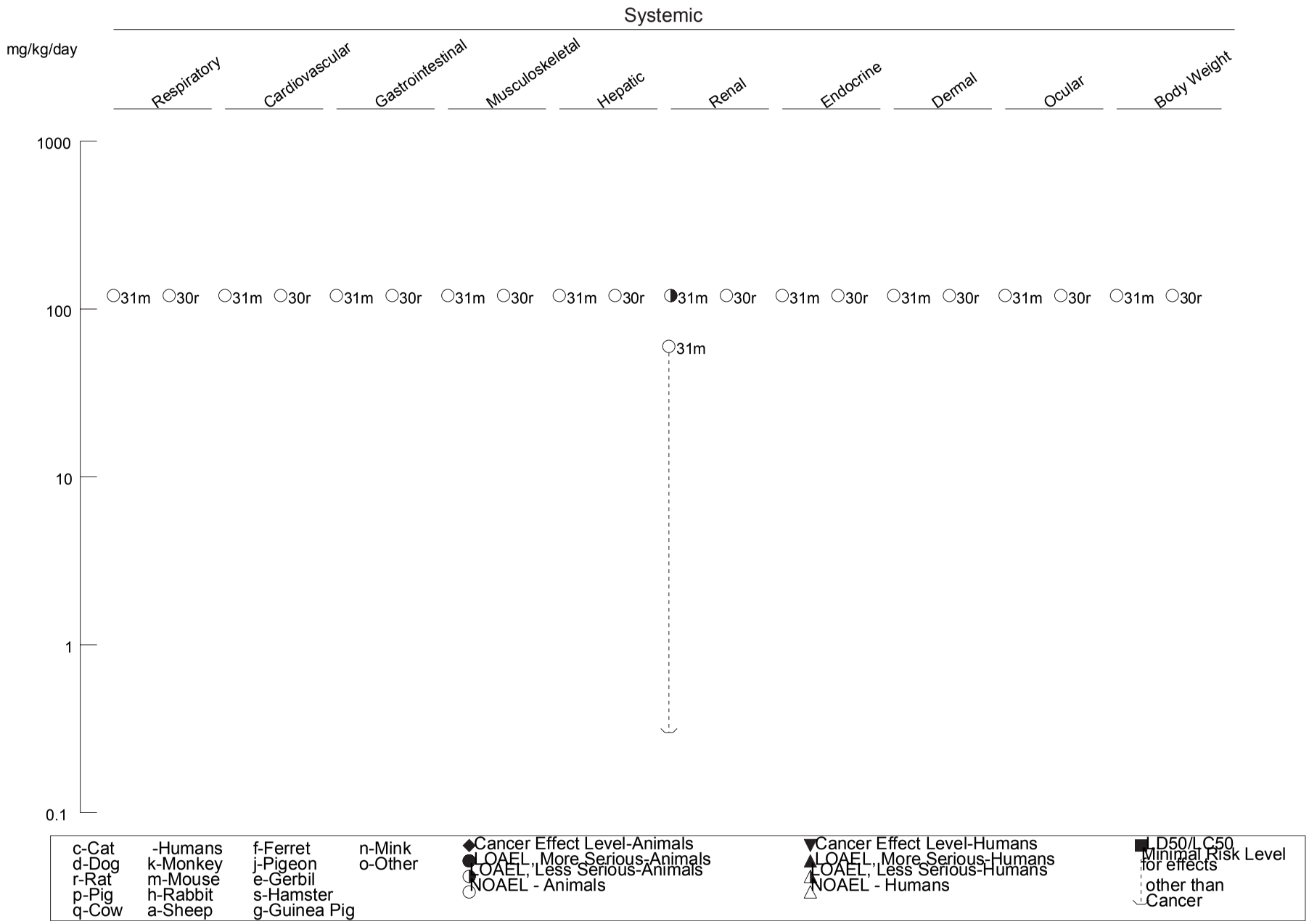


Figure 3-3 Levels of Significant Exposure to 1,2-dichlorobenzene - Oral *(Continued)*

Chronic (≥365 days)

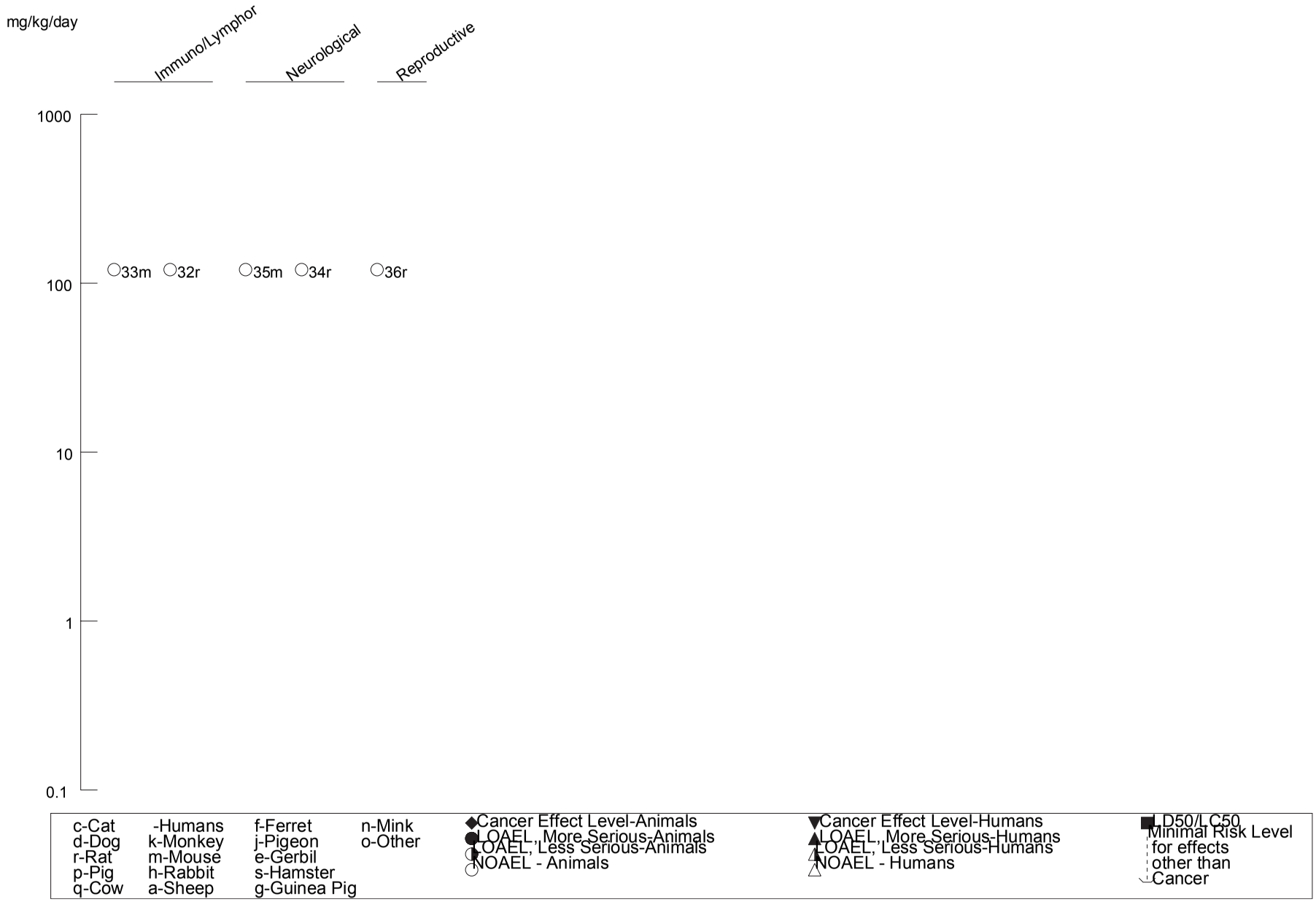


Table 3-4 Levels of Significant Exposure to 1,3-dichlorobenzene - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (G)				1200 M (14-day LD50) 1000[b] F (14-day LD50)	Monsanto 1980 1,3-dichlorobenzene	
Systemic								
2	Rat (Sprague-Dawley)	10 d 7 d/wk (GO)	Resp	735			McCauley et al. 1995 1,3-dichlorobenzene	
			Gastro	735				
			Hemato	735				
			Musc/skel	735				
			Hepatic	37[c] M 147 F	368 (increased liver weight, cytoplasmic vacuolization)			
					147 (increased liver weight)			
			Renal	735				
			Endocr	735				
			Dermal	735				
			Bd Wt	368	735 (reduced body weight gain)			
Immuno/ Lymphoret								
3	Rat (Sprague-Dawley)	10 d 7 d/wk (GO)		735			McCauley et al. 1995 1,3-dichlorobenzene	
Neurological								
4	Rat (Sprague-Dawley)	10 d 7 d/wk (GO)		735			McCauley et al. 1995 1,3-dichlorobenzene	

Table 3-4 Levels of Significant Exposure to 1,3-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
5	Rat (Sprague-Dawley)	10 d 7 d/wk (GO)		735			McCauley et al. 1995 1,3-dichlorobenzene	
Developmental								
6	Rat (Sprague-Dawley)	10 d Gd 6-15 (G)		200 F			Ruddick et al. 1983 1,3-dichlorobenzene	

Table 3-4 Levels of Significant Exposure to 1,3-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
7	Rat (Sprague-Dawley)	90 d 7 d/wk (GO)	Resp	588			McCauley et al. 1995 1,3-dichlorobenzene	
			Gastro	588				
			Hemato	37[b] M 147 F	147[b] M (increased leukocyte levels) 588 F (increased leukocyte levels)			
			Musc/skel	588				
			Hepatic		9[b] M (increased serum AST and cholesterol levels) 37 F (increased serum AST and cholesterol levels)			
			Renal	588				
			Endocr	9 F	9 M (reduced colloidal density in thyroid follicles) 147[d] M (increased cytoplasmic vacuolization in pituitary pars distalis) 37 F (reduced colloidal density in thyroid follicles)			
			Dermal	588				
			Bd Wt	147	588 (body weight gain was reduced 24% in males and 10% in females)			

Table 3-4 Levels of Significant Exposure to 1,3-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
8	Rat (Sprague-Dawley)	90 d 7 d/wk (GO)		588			McCauley et al. 1995 1,3-dichlorobenzene	
Neurological								
9	Rat (Sprague-Dawley)	90 d 7 d/wk (GO)		588			McCauley et al. 1995 1,3-dichlorobenzene	

a The number corresponds to entries in Figure 3-4

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Study result used to derive an acute-duration oral Minimal Risk Level (MRL) of 0.4 mg/kg/day for 1,3-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on liver weight data to select a point of departure, which was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

d Study result used to derive an intermediate-duration oral Minimal Risk Level (MRL) of 0.02 mg/kg/day for 1,3-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on incidences of pituitary lesions to select a point of departure, which was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

AST = aspartate aminotransferase; Bd Wt = body weight; d = day(s); Endocr = endocrine; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; ppm = parts per million; Resp = respiratory; wk = week(s)

Figure 3-4 Levels of Significant Exposure to 1,3-dichlorobenzene - Oral

Acute (≤14 days)

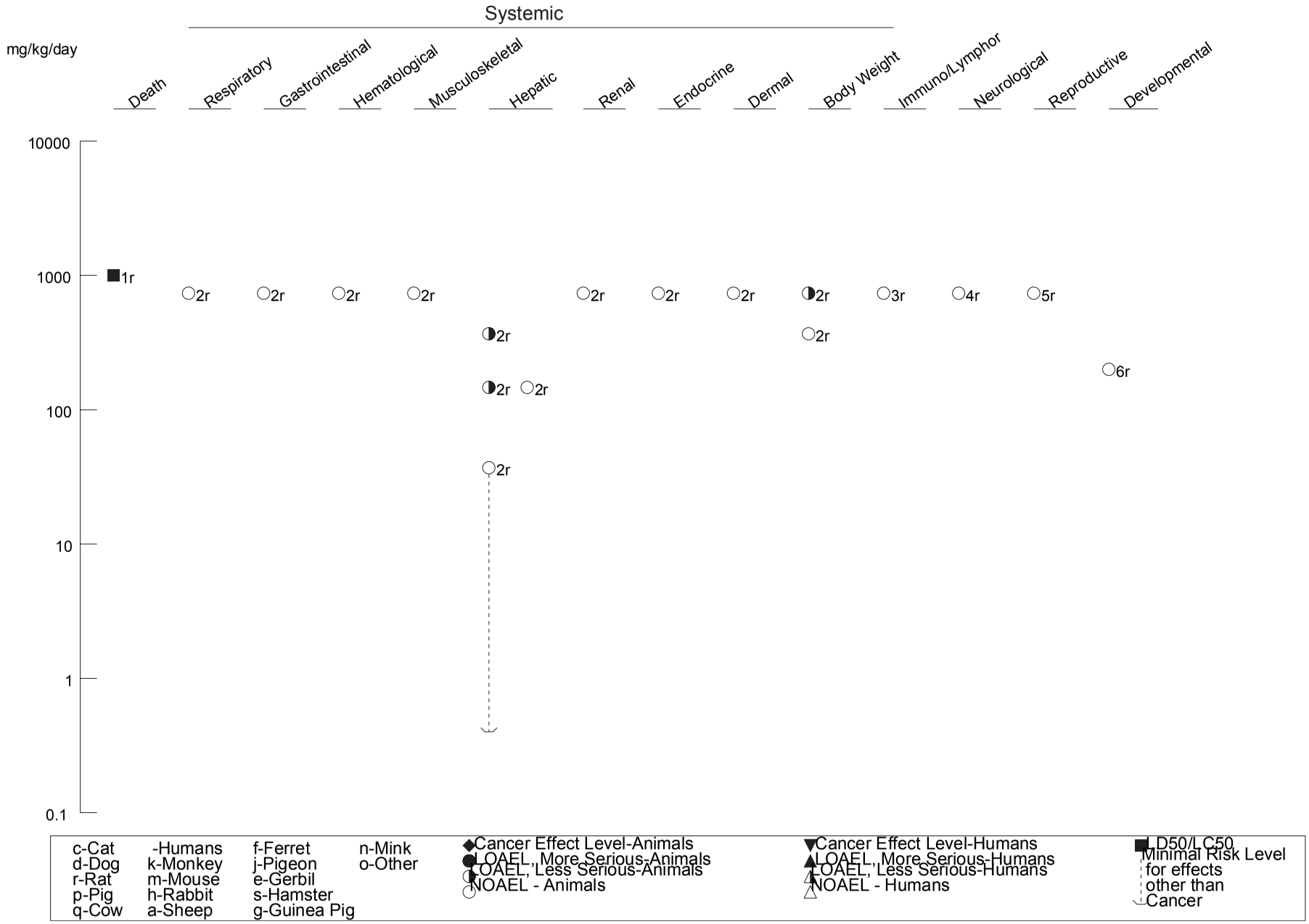


Figure 3-4 Levels of Significant Exposure to 1,3-dichlorobenzene - Oral *(Continued)*

Intermediate (15-364 days)

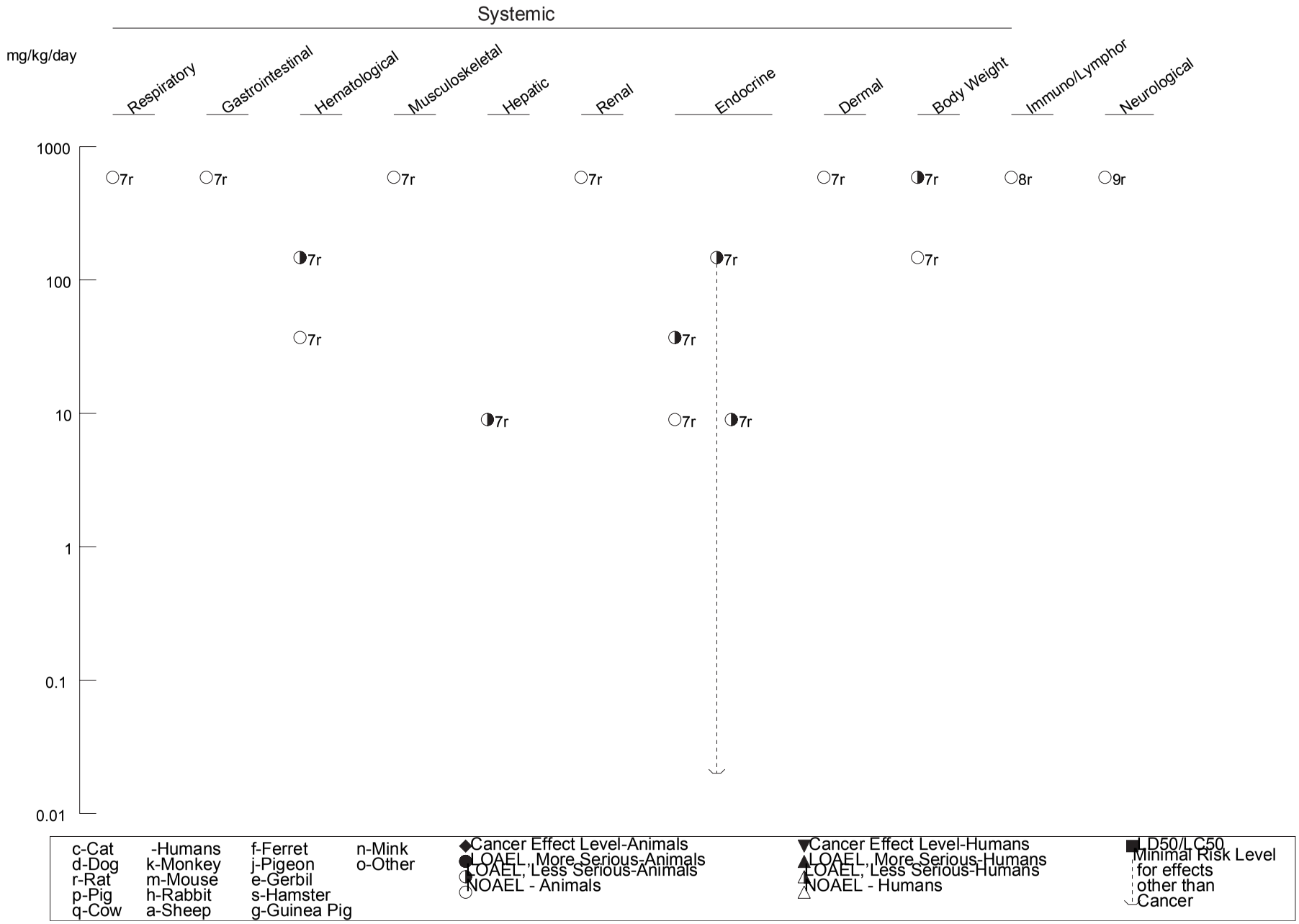


Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sherman)	once (GO)				3863 M (LD50) 3790[b] F (LD50)	Gaines and Linder 1986 1,4-dichlorobenzene	
2	Rat (NS)	once (GO)				4000 (LD100)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
3	Rat (Fischer- 344)	14 d 1 x/d (GO)				2000 M (5/5 males died) 1000[b] F (4/5 females died)	NTP 1987 1,4-dichlorobenzene	
4	Mouse (B6C3F1)	14 d 1 x/d (GO)				4000 (10/10 deaths by day 4)	NTP 1987 1,4-dichlorobenzene	
5	Gn Pig (NS)	once (GO)				2800 (LD100)	Hollingsworth et al. 1956 1,4-dichlorobenzene	
Systemic								
6	Rat (Fischer- 344)	once (GO)	Hemato	2790 M			Allis et al. 1992 1,4-dichlorobenzene	
			Hepatic		95 M (decreased relative liver weight)	475 M (centrilobular vacuolar degeneration)		
7	Rat (Wistar)	3 d 1 x/d (G)	Hepatic	250 F			Ariyoshi et al. 1975 1,4-dichlorobenzene	
			Bd Wt	250 F				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
8	Rat (albino)	14 d 1 x/d (GO)	Hepatic	10 M	20 M (increase in glucuronyl transferase and EPN detoxification activities)		Carlson and Tardiff 1976 1,4-dichlorobenzene	
9	Rat (albino)	14 d 1 x/d (GO)	Hepatic	300 M	650 M (increased serum isocitrate dehydrogenase)		Carlson and Tardiff 1976 1,4-dichlorobenzene	
10	Rat (albino)	14 d 1 x/d (GO)	Hepatic		650 M (decreased hexobarbital sleeping time; increased serum isocitrate dehydrogenase)		Carlson and Tardiff 1976 1,4-dichlorobenzene	
11	Rat (Fischer- 344)	once (GO)	Renal	500 F	500 M (protein droplet formation)		Charbonneau et al. 1987 1,4-dichlorobenzene	
12	Rat (Fischer- 344)	7 d 1 x/d (GO)	Renal		120 M (protein droplet formation)		Charbonneau et al. 1987 1,4-dichlorobenzene	
13	Rat (Fischer- 344)	once (GO)	Hepatic		600 F (increased liver weight)		Eldridge et al. 1992 1,4-dichlorobenzene	
			Bd Wt	600 F				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Fischer- 344)	once (GO)	Hepatic		600 F (centrilobular hepatocyte vacuolation)		Eldridge et al. 1992 1,4-dichlorobenzene	
15	Rat (Fischer- 344)	1 wk 5 d/wk 1 x/d (GO)	Hepatic	25 M	75 M (increased microsomal 7-pentaoxyresorufin O - depentylase activity)		Lake et al. 1997 1,4-dichlorobenzene	
			Renal	300 M				
			Bd Wt	150 M	300 M (approximately 10% decreased body weight gain)			
16	Rat (Fischer- 344)	14 d 1 x/d (GO)	Bd Wt	500[b] M 1000 F	1000 M (7-12% decrease in final body weight)		NTP 1987	
17	Rat (Fischer- 344)	14 d 1 x/d (GO)	Bd Wt	500	1000 (13.5% reduction in final body weight in males, 16.7% in females)		NTP 1987 1,4-dichlorobenzene	
18	Rat (albino)	5 d 1 x/d (G)	Hepatic			850 M (porphyria; degeneration of hepatocytes; focal necrosis)	Rimington and Ziegler 1963 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (albino)	5 d 1 x/d (G)	Hepatic			770 M (porphyria; degeneration of hepatocytes; focal necrosis)	Rimington and Ziegler 1963 1,4-dichlorobenzene	
			Bd Wt	770 M				
			Other		770 M (loss of appetite)			
20	Mouse (B6C3F1)	once (GO)	Hepatic		600 (increased liver weight)		Eldridge et al. 1992 1,4-dichlorobenzene	
			Bd Wt	600				
21	Mouse (B6C3F1)	once (GO)	Hepatic		600 (centrilobular hepatocyte vacuolation)		Eldridge et al. 1992 1,4-dichlorobenzene	
22	Mouse (B6C3F1)	1 wk 5 d/wk 1 x/d (GO)	Hepatic		300 M (increased relative liver weight)		Lake et al. 1997 1,4-dichlorobenzene	
			Renal	600 M				
			Bd Wt	600 M				
23	Mouse (B6C3F1)	14 d 1 x/d (GO)	Bd Wt	1000			NTP 1987 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Mouse (B6C3F1)	14 d 1 x/d (GO)	Bd Wt		250 M (13.3% reduction in final body weight)		NTP 1987 1,4-dichlorobenzene	
25	Mouse (B6C3F1)	4 d 1 x/d (GO)	Hepatic		300 (increased liver weight and hepatocyte proliferation)		Umemura et al. 1992 1,4-dichlorobenzene	
			Renal	600				
26	Mouse (B6C3F1)	once	Hepatic	1000 M	1800 M (increased ALT activity; severe centrilobular hepatocyte swelling)		Umemura et al. 1996 1,4-dichlorobenzene	
27	Mouse (B6C3F1)	once	Hepatic		1800 M (increased ALT activity; increased BrdU labeling)		Umemura et al. 1996 1,4-dichlorobenzene	
Neurological								
28	Rat (albino)	5 d 1 x/d (G)				770 M (clonic contractions; slight tremors; hemiparesis)	Rimington and Ziegler 1963 1,4-dichlorobenzene	
Reproductive								
29	Rat (CD)	10 d Gd 6-15 1 x/d (GO)		1000 F			Giavini et al. 1986 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
30	Rat (CD)	10 d Gd 6-15 1 x/d (GO)		250 F	500 F (increased incidence of fetuses with an extra rib)		Giavini et al. 1986 1,4-dichlorobenzene	
INTERMEDIATE EXPOSURE								
Death								
31	Rat (Fischer- 344)	13 wk 5 d/wk (GO)				1200[b] M (5/10 died) 1500 F (9/10 died)	NTP 1987 1,4-dichlorobenzene	
32	Mouse (B6C3F1)	13 wk 5 d/wk (GO)				1500 (3/10 males and 5/10 females died)	NTP 1987 1,4-dichlorobenzene	
Systemic								
33	Rat (NS)	30-120 d 1 x/d (GO)	Hepatic	200 F			Carlson 1977 1,4-dichlorobenzene	
34	Rat (Fischer- 344)	13 wk 5 d/wk (GO)	Hepatic		600 F (increased liver weight; hypertrophic centrilobular hepatocytes)		Eldridge et al. 1992 1,4-dichlorobenzene	
			Bd Wt	600 F				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Rat (NS)	192 d 5 d/wk (GO)	Hemato	188 F			Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Hepatic		188 F (slight increase in liver weight; not quantified)	376 F (slight cirrhosis, focal necrosis)		
			Renal		188 F (slight increase in kidney weight; not quantified)			
			Ocular	376 F				
36	Rat (Fischer- 344)	4 or 13 wk 5 d/wk 1 x/d (GO)	Hepatic	25 M	75 M (increased relative liver weight, induction of microsomal P450 and 7-pentoxyresorufin O-depentylase activity)		Lake et al. 1997 1,4-dichlorobenzene	
			Renal	75 M	150 M (increased relative kidney weight)			
			Bd Wt	75 M	150 M (approximately 10% decreased body weight gain)			
37	Rat (Wistar)	42 d Gd 1- pnd 21 (F)	Bd Wt	2 F			Makita et al. 2004, 2005 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
38	Rat (Fischer- 344)	13 wk 5 d/wk (GO)	Resp	600			NTP 1987 1,4-dichlorobenzene	
			Cardio	600				
			Gastro	600				
			Musc/skel	600				
			Hepatic	600				
			Renal	300[b] M	600 M (tubular degeneration)			
				600 F				
			Endocr	600				
			Dermal	600				
			Ocular	600				
			Bd Wt	600				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
39	Rat (Fischer- 344)	13 wk 5 d/wk (GO)	Resp	900	1200 (epithelial necrosis of nasal turbinates)		NTP 1987 1,4-dichlorobenzene	
			Cardio	1500				
			Gastro	900		1200 (epithelial necrosis of small intestine mucosa)		
			Hemato	300 F	300[b] M (slight decreases in RBC, HCT, and hemoglobin concentration)			
					600 F (decrease in mean corpuscular volume)			
			Musc/skel	1500				
			Hepatic	300[b] M 900 F	600 M (significant increase in serum cholesterol)	1200 (degeneration and necrosis of hepatocytes)		
			Renal	1500 F		300 M (necrosis of renal cortical tubular epithelium)		
			Endocr	1500				
			Dermal	1500				
			Ocular	900[b] M	1200[b] M (ocular discharge)			
				1200 F	1500 F (ocular discharge)			
			Bd Wt	900 F	300[b] M (11% decrease in final body weight)			
					1200 F (11% decrease in final body weight)			

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
40	Mouse (B6C3F1)	13 wk 5 d/wk (GO)	Hepatic	300	600 (increased liver weight; hypertrophic centrilobular hepatocytes)		Eldridge et al. 1992 1,4-dichlorobenzene	
			Bd Wt	600				
41	Mouse (B6C3F1)	4 or 13 wk 5 d/wk 1 x/d (GO)	Hepatic		300 M (increased relative liver weight; induction of microsomal 7-pentoxyresorufin O-depentylase activity)		Lake et al. 1997 1,4-dichlorobenzene	
			Renal	600 M				
			Bd Wt	600 M				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Mouse (B6C3F1)	13 wk 5 d/wk (GO)	Resp	1800			NTP 1987 1,4-dichlorobenzene	
			Cardio	1800				
			Gastro	1800				
			Hemato	1800 F	600 M (34% reduced WBC count)			
			Musc/skel	1800				
			Hepatic		600 (hepatocellular degeneration in 7/10 males and 9/10 females)			
			Renal	1800				
			Endocr	1800				
			Dermal	1800				
			Ocular	1800				
			Bd Wt		600 (final body weight reduced 13.9% in males and 10.3% in females)			

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Mouse (B6C3F1)	13 wk 5 d/wk (GO)	Resp	900			NTP 1987 1,4-dichlorobenzene	
			Cardio	900				
			Gastro	900				
			Hemato	900				
			Musc/skel	900				
			Hepatic	338	675 (moderate hepatocytomegaly in males and females)			
			Renal	900				
			Endocr	900				
			Dermal	900				
			Ocular	900				
			Bd Wt	900				
44	Dog	6 mo 5 d/wk 1 x/d (C)	Hemato	75			Naylor and Stout 1996 1,4-dichlorobenzene	
			Hepatic	10[c]	50 (increased serum alkaline phosphatase)			
			Bd Wt	75				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
45	Rabbit (NS)	219 d 92 doses (GO)	Hepatic		1000 (cloudy swelling, very few areas of focal necrosis)		Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Bd Wt		1000 (weight loss, not quantified)			
Immuno/ Lymphoret								
46	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		900		1200 (lymphoid depletion of thymus and spleen)	NTP 1987 1,4-dichlorobenzene	
47	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		1000		1500 (lymphoid necrosis in thymus; lymphoid depletion in the spleen; hematopoietic hypoplasia in spleen and bone marrow)	NTP 1987 1,4-dichlorobenzene	
Neurological								
48	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		900[b] M 1200 F		1200[b] M (tremors, poor motor response) 1500 F (tremors, poor motor response)	NTP 1987 1,4-dichlorobenzene	
49	Rabbit (NS)	219 d 92 doses (GO)				1000 (marked tremors)	Hollingsworth et al. 1956 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
50	Rat (Sprague-Dawley)	77-156 d 7 d/wk premating-lactation, two generations (GO)		270			Bornatowicz et al. 1994 1,4-dichlorobenzene	
51	Rat (Wistar)	42 d Gd 1- pnd 21 (F)		2 F			Makita et al. 2004, 2005 1,4-dichlorobenzene	
52	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		1500			NTP 1987 1,4-dichlorobenzene	
53	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		1800 M 1000 F[b]	1500 F (increase in relative ovary weight)		NTP 1987 1,4-dichlorobenzene	
Developmental								
54	Rat (Sprague-Dawley)	77-156 d 7 d/wk premating-lactation, two generations (GO)		30 F		90 F (increased postnatal/preweaning mortality in F1 and F2 pups)	Bornatowicz et al. 1994 1,4-dichlorobenzene	
55	Rat (Wistar)	42 d Gd 1- pnd 21 (F)		2			Makita et al. 2004, 2005 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Death								
56	Rat (Fischer- 344)	2 yr 5 d/wk (GO)				300 M (26/50 deaths)	NTP 1987 1,4-dichlorobenzene	
57	Dog	3 wk 5 d/wk 1 x/d (C)				150 (3/6 deaths)	Naylor and Stout 1996 1,4-dichlorobenzene	
58	Rabbit (NS)	367 d 5 d/wk (GO)				500 (some deaths; not quantified)	Hollingsworth et al. 1956 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
59	Rat (Fischer- 344)	2 yr 5 d/wk (GO)	Resp	300[b] M			NTP 1987 1,4-dichlorobenzene	
				600 F				
			Cardio	300[b] M				
				600 F				
			Gastro	300[b] M				
				600 F				
			Hemato	300[b] M				
				600 F				
			Musc/skel	300[b] M				
				600 F				
			Hepatic	300[b] M				
				600 F				
			Renal		150 M (moderate nephropathy)			
			Endocr	600 F	150 M (parathyroid hyperplasia)			
			Dermal	300[b] M				
				600 F				
			Ocular	300[b] M				
				600 F				
			Bd Wt	150[b] M	300[b] M (12.5% decrease in body weight gain)			
				300 F				
					600 F (12.4% decrease in body weight gain)			

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
60	Mouse (B6C3F1)	2 yr 5 d/wk (GO)	Resp	600			NTP 1987 1,4-dichlorobenzene	
			Cardio	600				
			Gastro	600				
			Hemato	600				
			Musc/skel	600				
			Hepatic		300 (hepatocellular degeneration, hepatocyte swelling and vacuolation)			
			Renal			300 (nephropathy, degeneration of cortical tubular epithelium)		
			Endocr	600 F	300 M (follicular cell hyperplasia in thyroid; adrenal medullary hyperplasia; focal hyperplasia of adrenal gland capsule)			
			Dermal	600				
			Ocular	600				
			Bd Wt	600				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
61	Dog	1 yr 5 d/wk 1 x/d (C)	Resp	75			Naylor and Stout 1996 1,4-dichlorobenzene	
			Cardio	75				
			Gastro	75				
			Hemato	50	75 (significantly reduced RBC in females and HCT)			
			Musc/skel	75				
			Hepatic	10[d]	50 (increases in serum alkaline phosphatase and liver weight, hepatocellular hypertrophy)			
			Renal	10	50 (suggestive collecting duct epithelial vacuolation)			
			Endocr	75				
			Dermal	75				
			Ocular	75				
			Bd Wt	75				

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
62	Rabbit (NS)	367 d 5 d/wk (GO)	Hepatic		500 (cloudy swelling, some areas of focal necrosis)		Hollingsworth et al. 1956 1,4-dichlorobenzene	
			Bd Wt		500 (weight loss, not quantified)			
Immuno/ Lymphoret								
63	Rat (Fischer- 344)	2 yr 5 d/wk (GO)		600			NTP 1987 1,4-dichlorobenzene	
64	Mouse (B6C3F1)	2 yr 5 d/wk (GO)			300 (lymphoid hyperplasia of lymph nodes)		NTP 1987 1,4-dichlorobenzene	
65	Dog	1 yr 5 d/wk 1 x/d (C)		75			Naylor and Stout 1996 1,4-dichlorobenzene	
Neurological								
66	Rat (Fischer- 344)	2 yr 5 d/wk (GO)		600			NTP 1987 1,4-dichlorobenzene	
67	Mouse (B6C3F1)	2 yr 5 d/wk (GO)		600			NTP 1987 1,4-dichlorobenzene	
68	Rabbit (NS)	367 d 5 d/wk (GO)				500 (marked tremors)	Hollingsworth et al. 1956 1,4-dichlorobenzene	

Table 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
69	Rat (Fischer- 344)	2 yr 5 d/wk (GO)		600			NTP 1987 1,4-dichlorobenzene	
70	Mouse (B6C3F1)	2 yr 5 d/wk (GO)		600			NTP 1987 1,4-dichlorobenzene	
Cancer								
71	Rat (Fischer- 344)	2 yr 5 d/wk (GO)				300 M (CEL: renal tubular cell adenoma and adenocarcinoma)	NTP 1987 1,4-dichlorobenzene	
72	Mouse (B6C3F1)	2 yr 5 d/wk (GO)				600 (CEL: hepatocellular adenoma and carcinoma)	NTP 1987 1,4-dichlorobenzene	

a The number corresponds to entries in Figure 3-5

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-5. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Study result used to derive an intermediate-duration oral minimal risk level (MRL) of 0.07 mg/kg/day for 1,4-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on serum alkaline phosphatase levels to select a point of departure, which was duration adjusted, then divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

d Study result used to derive a chronic-duration oral minimal risk level (MRL) of 0.07 mg/kg/day for 1,4-DCB, as described in detail in Appendix A. Benchmark dose analysis was performed on incidences of serum alkaline phosphatase levels to select a point of departure, which was duration adjusted, then divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ALT = alamine aminotransferase; Bd Wt = body weight; BrdU = Bromodeoxyuridine; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; EPN = O-ethyl O-p-nitrophenyl phenylphosphonothioate; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; HCT = hematocrit; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LD100 = lethal dose, 100% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; pnd = post-natal day; RBC = red blood cell; Resp = respiratory; x = time(s); WBC = white blood cell; wk = week(s); yr = year(s)

Figure 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral

Acute (≤14 days)

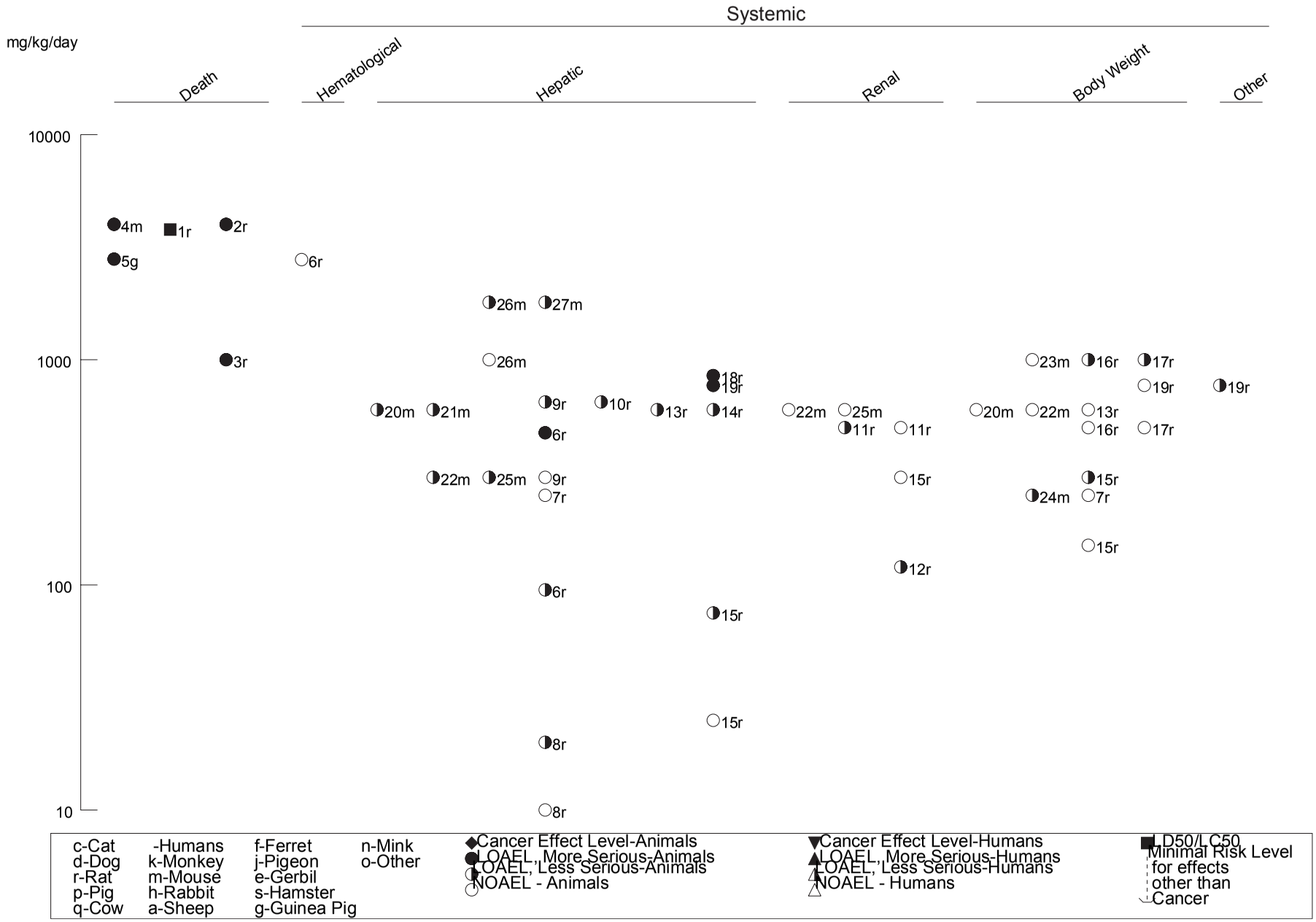


Figure 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral *(Continued)*

Acute (≤14 days)

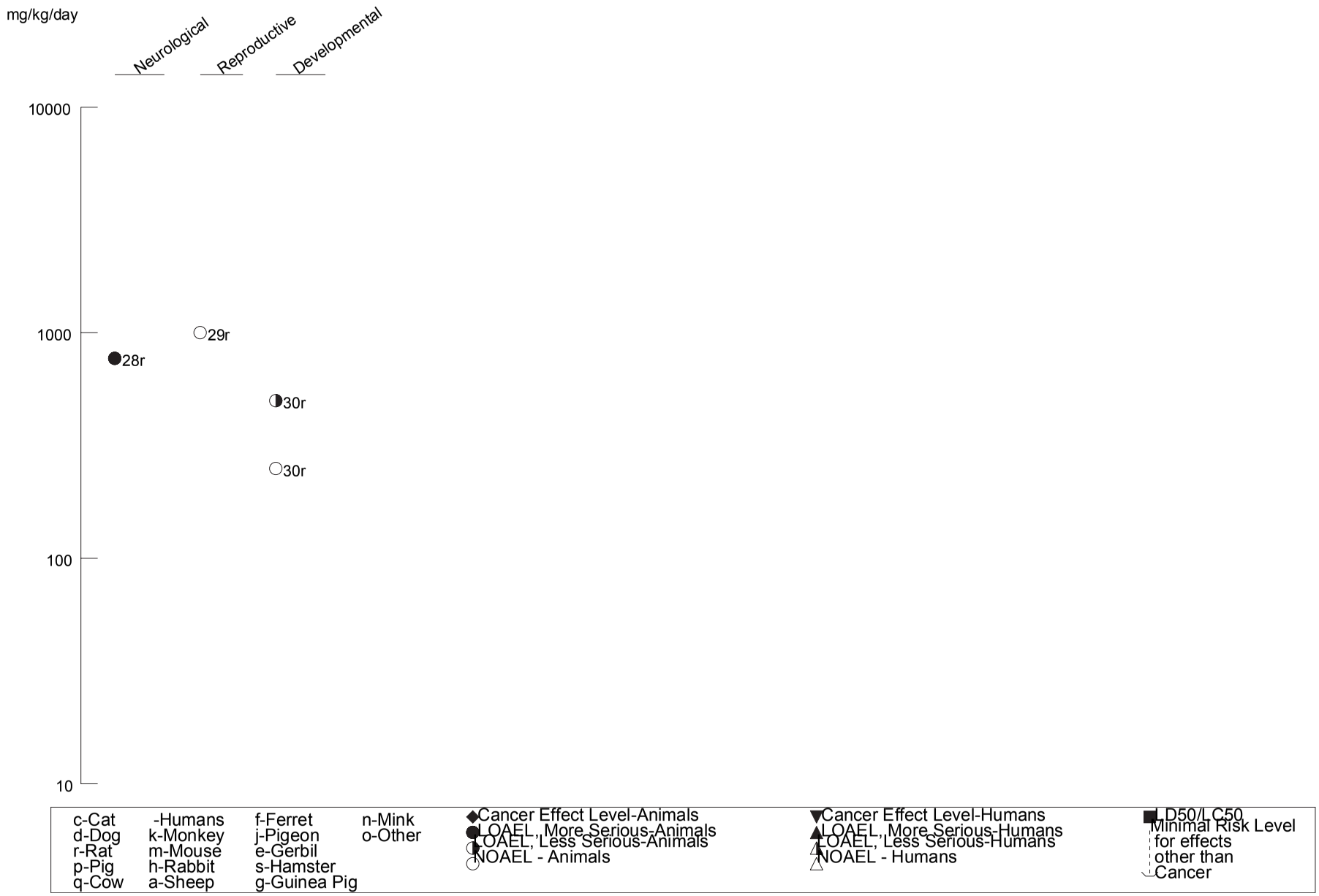


Figure 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral *(Continued)*

Intermediate (15-364 days)

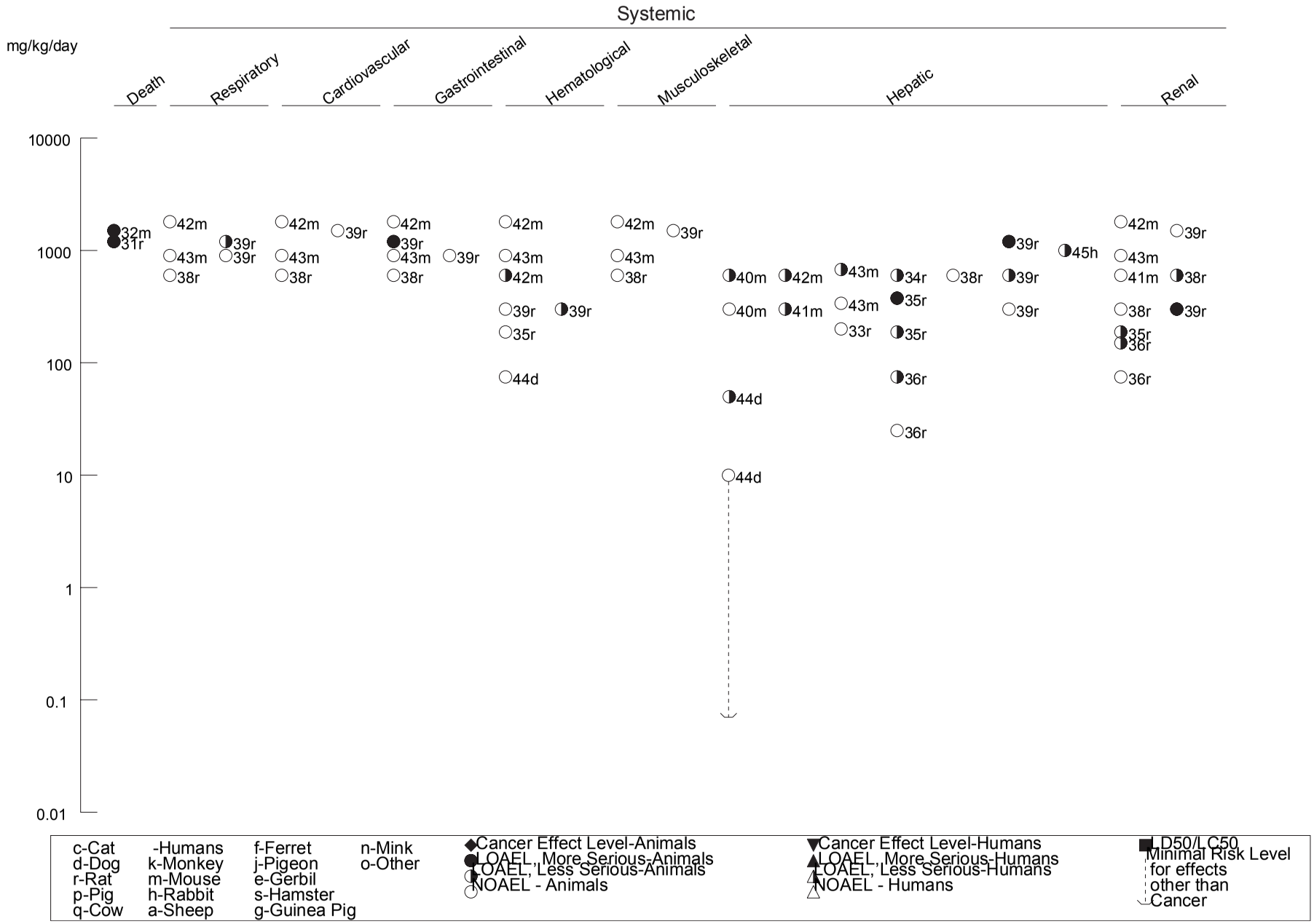


Figure 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral *(Continued)*

Intermediate (15-364 days)

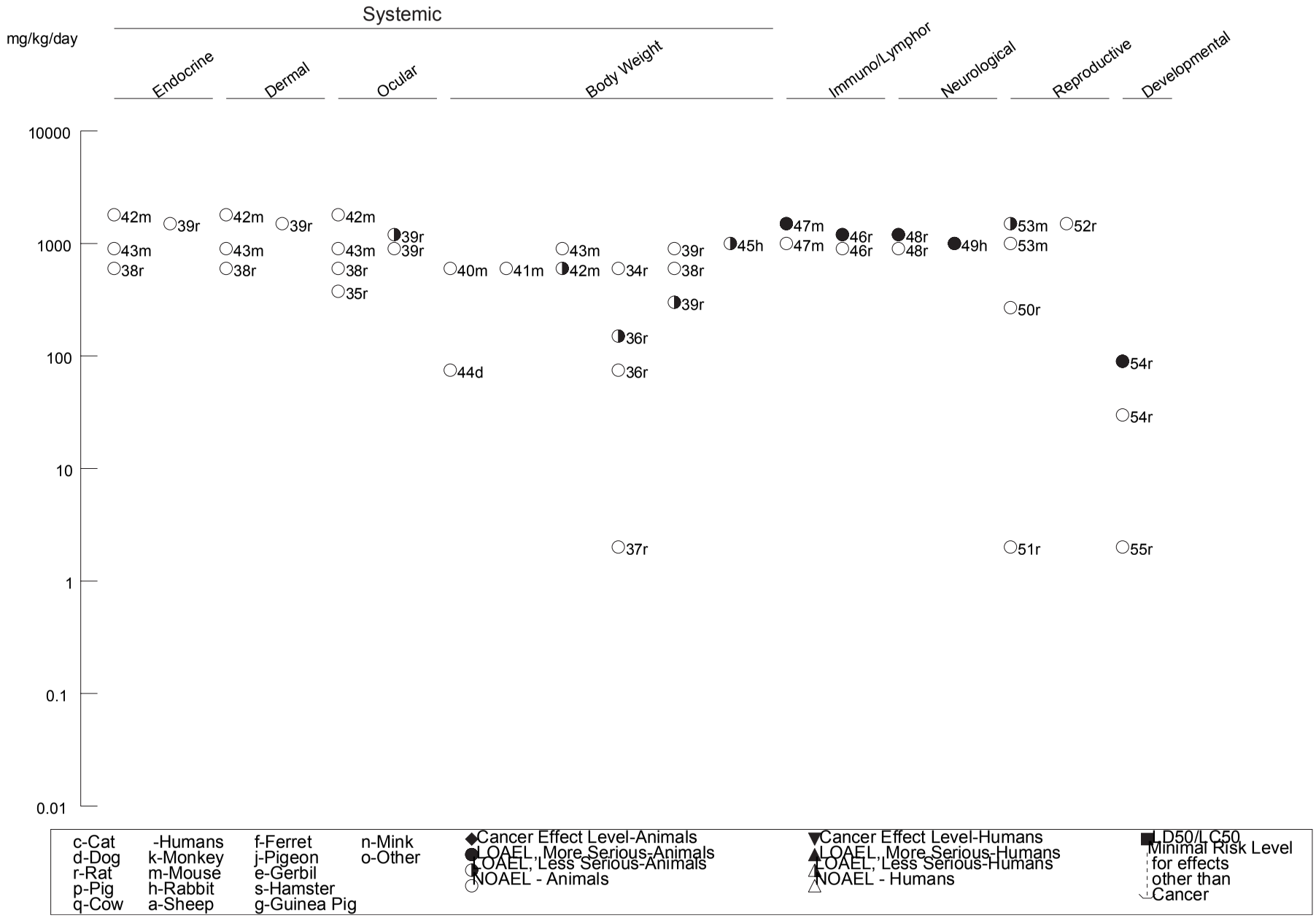


Figure 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral *(Continued)*

Chronic (≥365 days)

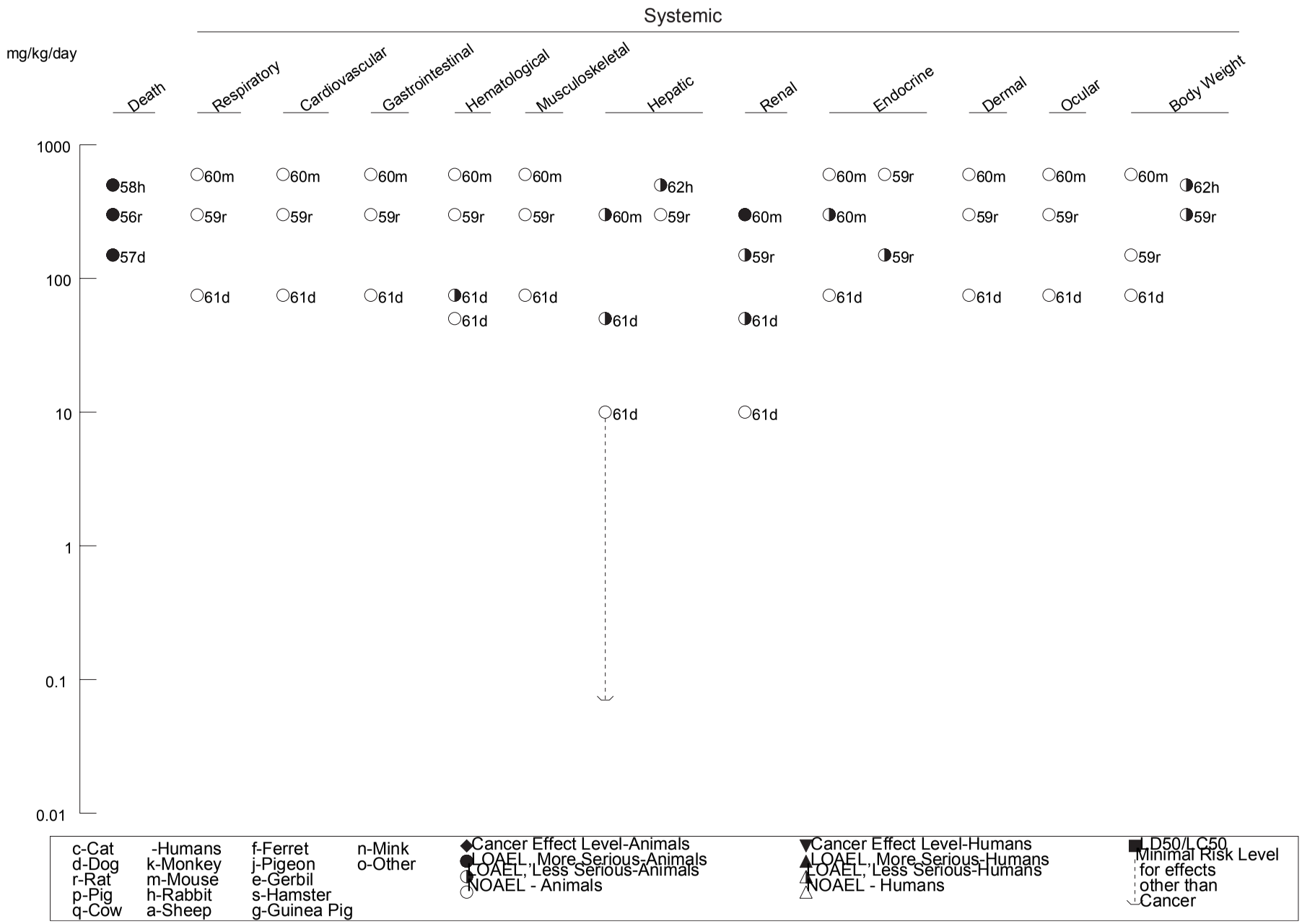
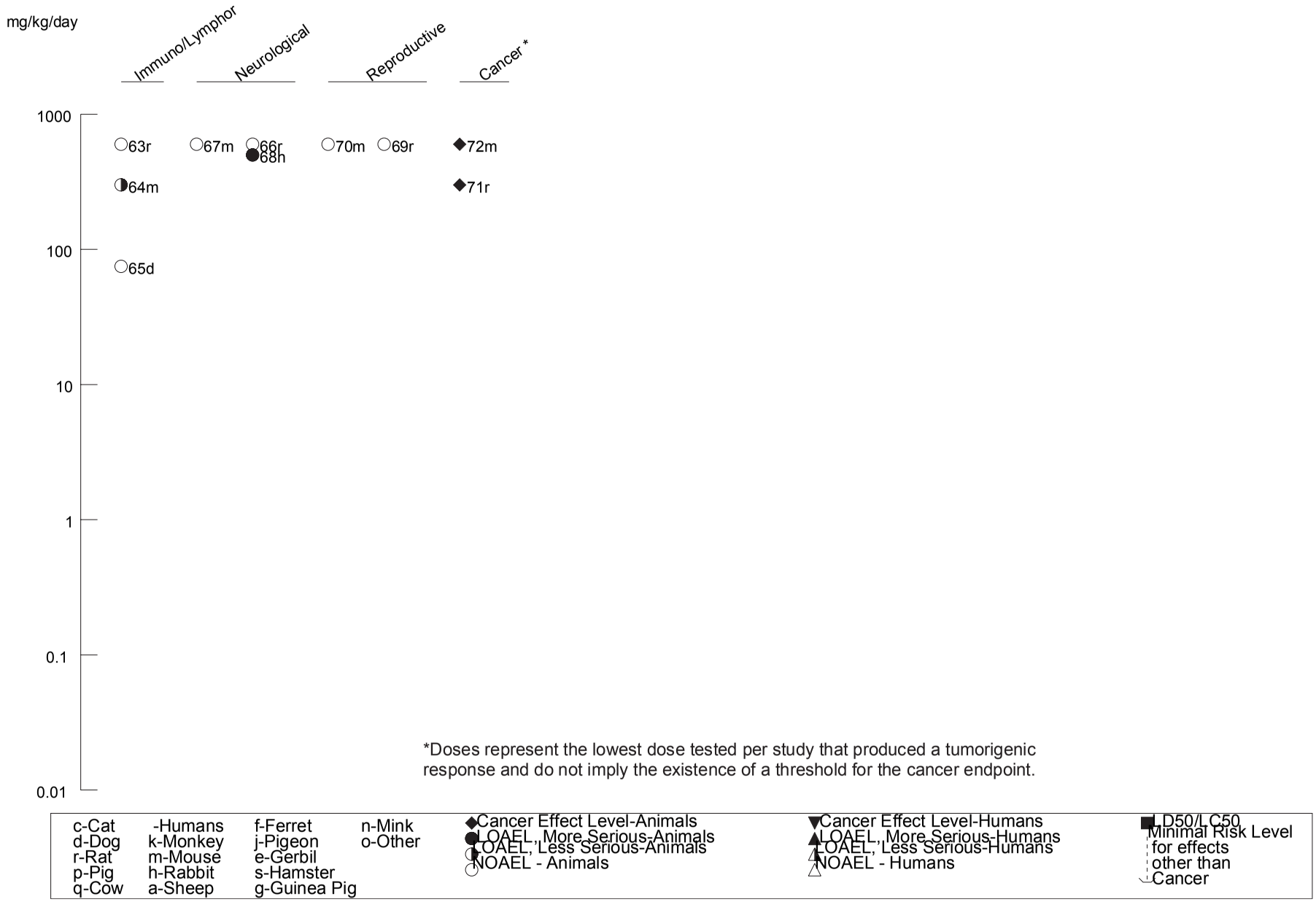


Figure 3-5 Levels of Significant Exposure to 1,4-dichlorobenzene - Oral *(Continued)*

Chronic (≥365 days)



Acute oral LD_{50} values of 1,200 and 1,000 mg/kg were determined in male and female Sprague-Dawley rats, respectively, administered a single dose of 1,3-DCB by gavage and observed for the following 14 days (Monsanto 1980).

No mortality or overt signs of toxicity occurred in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses as high as 735 mg/kg/day for 10 consecutive days, or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. No studies were located regarding death in humans after oral exposure to 1,4-DCB.

Animal mortality data for 1,4-DCB are available from acute-, intermediate-, and chronic-duration studies. In acute-duration animal studies, a single dose by gavage in olive oil of 1,000 mg/kg to rats and 1,600 mg/kg to guinea pigs resulted in no deaths, while a single dose of 4,000 mg/kg to rats and 2,800 mg/kg to guinea pigs resulted in 100% mortality (Hollingsworth et al. 1956). Similar results were seen in groups of adult male albino rats administered various doses of 1,4-DCB in corn oil once daily for 14 days; administration of 1,4-DCB at doses up to 600 mg/kg did not result in any deaths (Carlson and Tardiff 1976). Oral LD_{50} (lethal dose, 50% kill) values for adult Sherman rats administered 1,4-DCB in peanut oil were calculated to be 3,863 and 3,790 mg/kg for males and females, respectively (Gaines and Linder 1986). In contrast, groups of male F344 rats (n=1/group) were administered 13–27,900 mg/kg body weight in corn oil via gavage. Twenty-four hours after dosing, the animals were weighed and exsanguinated. No mortality among the 1,4-DCB-treated rats was observed (Allis et al. 1992).

In one series of studies (NTP 1987), the lethality data for 1,4-DCB, when administered for 14 days by gavage in corn oil to F344 rats and $B6C3F_1$ mice, were rather inconsistent. In one of these studies, no 1,4-DCB-related deaths occurred in rats of either sex that received doses up to 1,000 mg/kg/day; however, in the second rat study, four of five females (80%) at 1,000 mg/kg/day died, and all rats dosed at >2,000 mg/kg/day died. In one 14-day study in mice, no 1,4-DCB-related deaths occurred in either sex at levels up to 1,000 mg/kg/day; however, in a second 14-day mouse study, 70% of mice at 1,000 mg/kg/day died, and all mice that received 4,000 mg/kg/day died within 4 days. At 1,200 mg/kg/day, 5 of 10 male and 1 of 10 female rats died. No deaths occurred at 600 mg/kg/day.

In 13-week gavage studies, 17 of 20 rats (8 of 10 males and 9 of 10 females) dosed with 1,4-DCB in corn oil 5 days/week at 1,500 mg/kg/day died. When dosed in like manner with 1,200 mg/kg/day, 5 of

10 male and 1 of 10 female rats died. No deaths occurred at doses of ≤600 mg/kg/day (NTP 1987). Mortality rates in mice were somewhat lower; 8 of 20 (3 of 10 males and 5 of 10 females) animals dosed with 1,500 mg/kg/day 1,4-DCB in corn oil 5 days/week died. No deaths occurred in males or females at doses up to 900 and 1,000 mg/kg/day, respectively (NTP 1987).

High mortality was reported in male rats that received 1,4-DCB 5 days/week by gavage in corn oil in a 2-year study (NTP 1987). At 300 mg/kg/day, 26 of 50 males (52%) died; however, survival of female rats at 600 mg/kg/day was comparable to controls. There was no excess mortality in mice of either sex that received 1,4-DCB 5 days/week by gavage in corn oil for 2 years at levels up to 600 mg/kg/day (NTP 1987). The high rate of mortality in male rats was probably related, in part, to the severe nephrotoxic effects and renal tumors that were reported in these animals and are described in more detail in Sections 3.2.2.2 and 3.2.2.7.

Groups of five male and five female Beagle dogs were administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996). The 75 mg/kg/day dose is a time-weighted average level reflecting decreases from an initial high level of 150 mg/kg/day in response to severe toxicity. The main early effect was mortality during the first 25 days of the study; exposure to 150 mg/kg/day caused one male dog to be sacrificed *in extremis* on day 12, one male death on day 25, and one female death on day 24. With the exception of one control male that died on day 83, all remaining dogs survived exposure to 75 mg/kg/day.

3.2.2.2 Systemic Effects

Respiratory Effects.

1,2-Dichlorobenzene. No studies were located regarding respiratory effects in humans after oral exposure to 1,2-DCB.

No gross or histological changes were observed in the respiratory tract (nasal cavity, trachea, lungs, and/or bronchi) of Sprague-Dawley or F344 rats that were administered 1,2-DCB in corn oil by gavage in doses of 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991), ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985). There were no gross or histological effects in

the respiratory system of $B6C3F_1$ mice that were similarly treated with ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding respiratory effects in humans after oral exposure to 1,3-DCB.

No gross or histological changes were observed in the respiratory tract (nasal cavity and turbinates, lungs, and lower half of trachea) in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. No studies were located regarding respiratory effects in humans after oral exposure to 1,4-DCB.

In a series of dose range-finding studies, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987). At sacrifice, animals were examined grossly and major tissues were examined histologically. No compound-related effects were observed in the lungs at any dose up to 900 mg/kg/day, while rats treated with 1,200 mg/kg/day or higher exhibited epithelial necrosis of the nasal turbinates (NTP 1987). In parallel studies, $B6C3F_1$ mice were administered 1,4-DCB at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks. No compound-related effects were observed in the lungs at any dose level (NTP 1987).

In 2-year exposure studies in F344 rats, no respiratory effects were reported in males or females that received 1,4-DCB by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively (NTP 1987). In similarly dosed $B6C3F_1$ mice, no respiratory effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

Cardiovascular Effects.

1,2-Dichlorobenzene. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,2-DCB.

Mutifocal mineralization of the myocardial fibers of the heart (as well as skeletal muscle) was found in $B6C3F_1$ mice that were administered 500 mg/kg/day of 1,2-DCB in corn oil by gavage 5 days/week for 13 weeks (NTP 1985); this effect does not appear to have occurred in controls or lower dose groups (≤250 mg/kg/day). No gross or histological changes were observed in the heart of $B6C3F_1$ mice that were similarly treated with ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985), or in Sprague-Dawley or F344 rats that were similarly treated with 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991), ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,3-DCB.

No gross or histological changes in the aorta were observed in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,4-DCB.

In a series of dose range-finding studies, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987). At sacrifice, animals were examined grossly and major tissues were examined histologically. No compound-related cardiovascular effects were observed at any dose level. In parallel studies, $B6C3F_1$ mice were administered 1,4-DCB at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks. As with the rats, no compound-related cardiovascular effects were observed in mice at any of the doses used (NTP 1987).

In 2-year exposure studies in F344 rats, no cardiovascular effects were reported in males or females that received 1,4-DCB by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively (NTP 1987). In similarly dosed $B6C3F_1$ mice, no cardiovascular effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

No gross or histological changes were found in the aorta or heart of Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

Gastrointestinal Effects.

1,2-Dichlorobenzene. No studies were located regarding gastrointestinal effects in humans after oral exposure to 1,2-DCB.

No gross or histological changes were observed in the gastrointestinal tract (esophagus, stomach, small intestine, colon, and/or other tissues) of Sprague-Dawley or F344 rats that were administered 1,2-DCB in corn oil by gavage in doses of 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985). Additionally, there were no gross or histological effects in the gastrointestinal tract of $B6C3F_1$ mice that were similarly treated with ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding gastrointestinal effects in humans after oral exposure to 1,3-DCB.

No gross or histological changes were observed in the gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, tongue) in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days, or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. No studies were located regarding gastrointestinal effects in humans after oral exposure to 1,4-DCB.

In a series of dose range-finding studies, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987). At sacrifice, animals were examined grossly and major tissues were examined histologically. Gastrointestinal effects were observed at doses of 1,200 mg/kg/day or more and consisted of epithelial necrosis and villar bridging of the mucosa of the small intestines. No gastrointestinal effects were noted in rats treated with 1,4-DCB at doses of 900 mg/kg/day or less (NTP 1987). In parallel

studies with B6C3F$_1$ mice, no compound-related gastrointestinal effects were observed after administration of 1,4-DCB at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987).

In 2-year exposure studies in Fischer 344 rats, no gastrointestinal effects were reported in males or females that received 1,4-DCB by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively (NTP 1987). In similarly dosed B6C3F$_1$ mice, no gastrointestinal effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

No gross or histological changes were found in the gastrointestinal tract of Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996). Nine regions of the gastrointestinal tract were examined.

Hematological Effects.

1,2-Dichlorobenzene. No studies were located regarding hematological effects in humans after oral exposure to 1,2-DCB.

No hematological changes were observed in Sprague-Dawley or F344 rats that were administered 1,2-DCB in corn oil by gavage in doses of ≤300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), ≤400 mg/kg/day for 90 consecutive days (Robinson et al. 1991), or ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985). Additionally, there were no hematological effects in B6C3F$_1$ mice that were similarly treated with ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding hematological effects in humans after oral exposure to 1,3-DCB.

No hematological changes (numbers of erythrocytes and leukocytes, hemoglobin level, hematocrit, or mean corpuscular volume) were observed in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days, or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. A 21-year-old pregnant woman who had eaten 1–2 blocks of 1,4-DCB toilet air freshener per week throughout pregnancy developed severe microcytic, hypochromic anemia with

excessive polychromasia and marginal nuclear hypersegmentation of the neutrophils. Heinz bodies were seen in a small number of the red cells. After she discontinued this practice (at about 38 weeks of gestation), her hemoglobin levels began to rise steadily. She gave birth to a normal infant with no hematological problems, and her own red blood cells were again normal at the final check 6 weeks after delivery (Campbell and Davidson 1970). Acute hemolytic anemia and were reported to have occurred in a 3-year-old boy who had played with 1,4-DCB crystals (Hallowell 1959). It is not clear whether this child had actually ingested any of the 1,4-DCB crystals.

Hematological effects reported in animal studies mainly concern effects on red cells in rats and on white cells in mice. Groups of male F344 rats (n=1/group) were administered 13–2,790 mg/kg body weight of 1,4-DCB once via corn oil gavage. Twenty-four hours after dosing, the animals were weighed and exsanguinated. No hematological alterations were noted in any of the treated rats (Allis et al. 1992).

No adverse effects on hemoglobin levels or hematocrit were seen in adult male albino rats dosed with 1,4-DCB by gavage in corn oil at levels up to 40 mg/kg/day for 90 days (Carlson and Tardiff 1976).

In F344 rats administered 1,4-DCB by gavage in corn oil, 7 days/week for 13 weeks at doses of 75–600 mg/kg/day, no compound-related hematological effects were noted (Bomhard et al. 1988). In a series of experiments performed by Hollingsworth et al. (1956), male rats were administered 1,4-DCB by gavage in olive oil at doses of 10–500 mg/kg/day, 5 days/week for 4 weeks; female rats received 1,4-DCB in like manner at doses of 18.8–376 mg/kg/day, 5 days/week for 192 days; and male and female rabbits received 500 mg/kg/day 1,4-DCB, 5 days/week for 367 days. Administration of 1,4-DCB produced no hematological effects at any dose.

In another 13-week study in F344 rats, male rats that received 1,4-DCB at 300 mg/kg/day and above had decreased hematocrit levels, red blood cell counts, and hemoglobin concentrations (NTP 1987). None of these hematologic effects were consistently seen in female rats at the same dosage level; however, a decrease in mean corpuscular volume was noted in females at doses of 600 mg/kg/day or more. In a parallel study in male and female $B6C3F_1$ mice dosed with 84.4–900 mg/kg/day 1,4-DCB for 13 weeks, no hematological effects were noted in male or female mice at doses up to 900 mg/kg/day (NTP 1987); however, in another study, $B6C3F_1$ mice dosed with 600–1,800 mg/kg/day 1,4-DCB for 13 weeks showed hematologic effects including 34–50% reductions in the white cell counts in all male dose groups; these decreases were accompanied by 26–33% decreases in lymphocytes and 69–82% decreases in neutrophils. No hematological effects were noted in female $B6C3F_1$ mice at doses up to 1,800 mg/kg/day (NTP 1987).

No hematologic effects were reported in 2-year studies in which male F344 rats received 1,4-DCB at levels up to 300 mg/kg/day/day and female rats received levels up to 600 mg/kg/day (NTP 1987). Similar results were reported in $B6C3F_1$ mice of both sexes exposed to 600 mg/kg/day 1,4-DCB for 2 years (NTP 1987).

Hematology was evaluated in groups of five male and five female Beagle dogs that were administered 1,4-DCB by capsule in doses of 0, 10, 50, or 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996). Ten routine indices and one blood clotting measurement (activated partial thromboplastin time) were evaluated at 6 and 12 months. A mild anemia, as indicated by significantly reduced red blood cell count in females and hematocrit in males, was observed after 6 months at 75 mg/kg/day, but resolved by the end of the study. Histological findings in the bone marrow (erythroid hyperplasia in females) and spleen (excessive hematopoiesis and megakaryocyte proliferation in both sexes) at 75 mg/kg/day indicated a compensatory response to the earlier anemia.

Musculoskeletal Effects.

1,2-Dichlorobenzene. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,2-DCB.

Mutifocal mineralization of the myocardial fibers of the heart and skeletal muscle was found in $B6C3F_1$ mice (3/10 males, 8/10 females) that were administered 500 mg/kg/day of 1,2-DCB in corn oil by gavage 5 days/week for 13 weeks (NTP 1985); this effect does not appear to have occurred in controls or lower dose mice (≤250 mg/kg/day). No gross or histological changes were observed in muscle of $B6C3F_1$ mice that were similarly treated with ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985), or in Sprague-Dawley or F344 rats that were similarly treated with 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

No gross or histological changes in bone were observed in any of the rat or mouse 10-day, 13-week, or 103-week studies summarized above (NTP 1985; Robinson et al. 1991).

1,3-Dichlorobenzene. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,3-DCB.

No gross or histological changes were observed in thigh muscle or sternebrae in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,4-DCB.

In a series of dose range-finding studies, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks. At sacrifice, animals were examined grossly and major tissues were examined histologically. No musculoskeletal effects were noted in any of the 1,4-DCB-treated rats. In parallel studies with $B6C3F_1$ mice, no compound-related musculoskeletal effects were observed after administration of 1,4-DCB at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987).

In 2-year exposure studies in F344 rats, no musculoskeletal effects were reported in males or females that received 1,4-DCB by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively. In similarly dosed $B6C3F_1$ mice, no musculoskeletal effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

No gross or histological changes were found in skeletal muscle or bone of Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

Hepatic Effects.

1,2-Dichlorobenzene. No studies were located regarding hepatic effects in humans after oral exposure to 1,2-DCB.

The liver is a main target of toxicity in animals following oral exposure to 1,2-DCB. Necrosis and other degenerative hepatic changes were observed in acute-duration studies in which 1,2-DCB was administered in oil by gavage. A single 1,500 mg/kg dose (a lethal level) caused central necrosis of the liver in rats (number and gender not reported) (DuPont 1982). Severe liver damage, characterized by

intense necrosis and fatty changes, occurred in three male rats administered 455 mg/kg/day for 15 consecutive days (Rimington and Ziegler 1963). Other hepatic effects in this study included porphyria, manifested as increased mean peak urinary levels of coproporphyrin, uroporphyrin, porphobilinogen (PBG), and γ-aminolevulinic acid (ALA) that were approximately 10-fold higher than levels in controls. Liver changes in other acute-duration studies included necrosis and increased serum ALT in rats given 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991). The necrosis was slight in severity and significantly (p=0.04) increased in males at 300 mg/kg/day [4/10 compared to 0/10 in controls; incidences in lower dose groups (37.5, 75, and 150 mg/kg/day) were not specifically reported and are assumed to be 0/10]. Incidences of other hepatic lesions were not significantly increased but included inflammation (characterized by lymphocyte and macrophage infiltrates) and degeneration of hepatocytes (characterized varying degrees of fibrillar or vacuolated cytoplasm and swelling with intact cell membranes). Liver weight was increased in females at ≥150 mg/kg/day and males at 300 mg/kg/day; the increased liver weight in female rats in this study (Robinson et al. 1991) was selected as the critical effect for deriving an acute-duration oral MRL of 0.7 mg/kg/day for 1,2-DCB. No liver histopathology was observed in male or female rats that were given doses as high as 500 or 1,000 mg/kg/day for 14 consecutive days (NTP 1985). The inconsistency between these findings and those of Robinson et al. (1991) might be due to a small number of animals (5 rats/sex/dose level) in the NTP (1985) study and mild response (low incidence and severity of lesions) in the Robinson et al. (1991) study. Hepatic degeneration and necrosis were observed in mice exposed to 250 or 500 mg/kg/day for 14 consecutive days (NTP 1985), but this study is also limited by small numbers of animals (3–4 mice/sex/group).

Liver histopathology was also the predominant finding in intermediate-duration studies of rats and mice exposed to 1,2-DCB (Hollingsworth et al. 1958; NTP 1985; Robinson et al. 1991). The compound was administered in oil vehicle by gavage in all of these studies. Slight to moderate cloudy swelling of the liver was found in female rats (strain not specified) dosed with 376 mg/kg/day, 5 days/week for 138 doses in 192 days, but not at lower dose levels of 18.8 or 188 mg/kg/day (Hollingsworth et al. 1958). The incidence of the lesion was not reported. Liver weight was increased at ≥188 mg/kg/day, but it is unclear whether this is an adaptive change or adverse effect due to the lack of histological or other evidence of tissue damage.

Administration of 400 mg/kg/day for 90 consecutive days caused significantly increased incidences of lesions in Sprague-Dawley rats, including centrilobular degeneration, centrilobular hypertrophy, and single cell necrosis in 10/10, 9/10, and 7/10 males, respectively, and 8/10, 10/10, and 5/10 females, respectively (Robinson et al. 1991). Histology was not evaluated at other dose levels (25 or

100 mg/kg/day), although no lesions occurred in controls of either sex. Absolute and relative liver weights and serum levels of ALT were significantly increased at ≥100 mg/kg/day, but the increases in ALT were not dose-related and other liver-associated enzymes (AST, LDH, AP) were not increased. The 400 mg/kg/day dose is a LOAEL for hepatic effects based on histopathology. A reliable NOAEL cannot be identified because histology was not evaluated at lower doses, the increase in serum ALT was not dose-related or supported by changes in other serum indicators of liver damage, and an increase in liver weight without clear evidence of tissue damage is considered to be an adaptive response.

NTP (1985) conducted subchronic studies in F344/N rats and $B6C3F_1$ mice to determine doses to be used in chronic bioassays. Groups of 10 males and 10 females of each species were administered 1,2-DCB in doses of 0, 30, 60, 125, 250, or 500 mg/kg/day, 5 days/week for 13 weeks. Histology examinations of the liver were limited to the control and three highest dose groups. Degenerative lesions were significantly ($p \leq 0.05$) increased in both species at ≥250 mg/kg/day. Changes in the rats included necrosis of individual hepatocytes at ≥250 mg/kg/day and centrilobular degeneration at 500 mg/kg/day; total incidences of these lesions at 0, 125, 250, and 500 mg/kg/day were 0/10, 1/10, 4/9, and 8/10 in males, respectively, and 0/10, 3/10, 5/10, and 7/8 in females, respectively. Relative liver weight was significantly increased at ≥125 mg/kg/day in both sexes, but there were no increases in serum levels of liver enzymes (ALT, AP, or gamma-glutamyltranspeptidase [GGPT]) at any dose. Serum cholesterol was significantly increased in males at ≥30 mg/kg/day (50.0, 17.6, 26.5, 70.6, and 109% higher than controls in the low to high dose groups, not significant at 42.9 mg/kg/day) and females at ≥125 mg/kg/day (12.2, 12.2, 32.6, 26.5, and 51.0%). Urinary concentrations of uroporphyrin and coproporphyrin were 3–5 times higher than controls in the 500 mg/kg/day males and females, but this increase was not considered indicative of porphyria because total porphyrin concentration in the liver was not altered at any dose level and no pigmentation indicative of porphyria was observed by ultraviolet light at necropsy. The increases in relative liver weight seen in male and female rats at 125 mg/kg/day are believed to represent the beginning of adverse hepatic effects, indicating that 125 mg/kg/day is a minimal LOAEL for this study. The increased liver weight in the female rats in this study (NTP 1985) was selected as the critical effect for deriving an intermediate-duration oral MRL of 0.6 mg/kg/day for 1,2-DCB. In the mice, no compound-related histopathological changes were observed in either sex at 0 and 125 mg/kg/day, or in females at 250 mg/kg/day. Lesions that were significantly increased included necrosis of individual hepatocytes, hepatocellular degeneration and/or pigment deposition in 4/10 males at 250 mg/kg/day, and centrilobular necrosis, necrosis of individual hepatocytes, and/or hepatocellular degeneration in 9/10 males and 9/10 females at 500 mg/kg/day. Relative liver weights were significantly increased at 500 mg/kg/day in both sexes, but there were no exposure-related changes in serum levels of ALT, AP, or GGPT in either

sex at any dose (no other clinical chemistry indices were examined in the mice). The hepatic histopathology findings indicate that the NOAEL and LOAEL for liver effects in mice are 125 and 250 mg/kg/day, respectively.

In the NTP (1985) chronic study, groups of 50 male and 50 female F344/N rats and $B6C3F_1$ mice were administered 1,2-DCB in corn oil by gavage in doses of 0, 60, or 120 mg/kg/day, 5 days/week for 103 weeks. Histopathological examinations were performed in all animals, although liver weights and clinical chemistry indices were not evaluated. There were no exposure-related nonneoplastic liver lesions in either species, indicating that 125 mg/kg/day is the chronic NOAEL for liver effects in both rats and mice.

1,3-Dichlorobenzene. No studies were located regarding hepatic effects in humans after oral exposure to 1,3-DCB.

Liver toxicity was evaluated in groups of 10 male and 10 female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by daily gavage, in doses of 0, 37, 147, 368, or 735 mg/kg/day for 10 consecutive days, or 9, 37, 147, or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995). Study end points included serum chemistry indices (AP, AST, ALT, LDH, cholesterol), liver weight, and gross appearance and histology of the liver. As discussed below, hepatic changes were found at ≥147 mg/kg/day in the 10-day study and ≥9 mg/kg/day in the 90-day study.

Hepatic effects in the 10-day rat study included significantly ($p \leq 0.05$) increased relative liver weight in males at ≥147 mg/kg/day and females at ≥368 mg/kg/day (absolute organ weight not reported), and histopathology at ≥368 mg/kg/day in both sexes. Increased liver weight in this study (McCauley et al. 1995) was selected as the critical effect for deriving an acute-duration oral MRL of 0.4 mg/kg/day for 1,3-DCB. The main hepatic histological change was dose-related centrilobular hepatocellular degeneration, characterized by varying degrees of cytoplasmic vacuolization and swelling with intact membranes. Respective incidences of this lesion at 368 and 735 mg/kg/day were 2/10 and 9/10 in males, and 6/10 and 10/10 females; incidences in the other groups were not reported, but are presumed to be 0/10. Other hepatic alterations included hepatocellular necrosis that was sporadically noted in the 147, 368, and 735 mg/kg/day groups. This change was usually minimal to mild, and tended to increase in incidence and severity in the males in a dose-related manner; however, incidences were not reported. Cholesterol was the only serum end point that had values exceeding the reference range. Serum

cholesterol was significantly increased at 368 and 735 mg/kg/day in both sexes, but this change could be pituitary-related (see discussion of the 90-day study in Endocrine Effects).

Hepatic effects in the 90-day study included significantly increased relative liver weight (absolute weight not reported) and histopathological changes at ≥147 mg/kg/day in both sexes. The liver lesions included inflammation, hepatocellular alterations (characterized by spherical, brightly eosinophilic homogeneous inclusions), and hepatocellular necrosis. Liver lesions that were significantly increased included hepatocellular cytoplasmic alterations of minimal to mild severity in males at ≥147 mg/kg/day (incidences in the control to high dose groups were 1/10, 2/10, 1/10, 6/10, and 7/9) and females at 588 mg/kg/day (0/10, 2/10, 0/10, 1/10, and 7/9), and necrotic hepatocyte foci of minimal severity in both sexes at 588 mg/kg/day (1/10, 2/10, 1/10, 2/10, and 5/9 in males, and 0/10, 0/10, 0/10, 3/10, and 5/9 in females). Other statistically significant liver-associated effects included significantly increased serum AST levels (90–100% higher than controls) in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day. Serum LDH levels were also reduced in males at ≥9 mg/kg/day, but the biological significance of a decrease in liver enzymes is unclear. Serum cholesterol values were significantly increased in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day, but this change could be pituitary-related (see Endocrine Effects).

1,4-Dichlorobenzene. A single case study was located regarding hepatic effects in humans after oral exposure to 1,4-DCB. In this case report, the author describes a 3-year-old boy who had been playing with crystals containing 1,4-DCB for 4–5 days before being admitted to the hospital. On admission, the boy was jaundiced and his mucous membranes were pale. After a blood transfusion, the child gradually improved. It was unclear whether the boy actually ingested any of the 1,4-DCB (Hallowell 1959).

The acute hepatotoxicity and response of hepatic cytochrome P-450 in response to dosing with 1,4-DCB were evaluated in groups of male F344 rats (n=1/group) given one dose of 13–2,790 mg/kg body weight by corn oil gavage. Twenty-four hours after dosing, the animals were weighed and sacrificed. Serum was collected and analyzed for total bilirubin, cholesterol, AST, alanine aminotransferase (ALT), and alkaline phosphatase. The liver was weighed and slices examined histopathologically. Liver microsomes were prepared and assayed for P-450, in addition to liver protein determinations. 1,4-DCB did not produce liver necrosis at any dose. There was also no effect observed on serum levels of ALT and AST. Hepatic cytochrome P-450 levels were increased about 30% by 1,4-DCB beginning at 380 mg/kg and remaining elevated at all higher doses. No consistent pattern of change was found for indicators of

hepatobiliary damage, serum cholesterol, serum alkaline phosphatase, and total bilirubin (Allis et al. 1992).

The effects of 1,4-DCB were compared in male F344 rats given 0 (corn oil control), 25, 75, 150, and 300 mg/kg/day 1,4-DCB (n=6–8/group/time) by daily oral gavage 5 days/week for 1 week. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing 5-bromo-2'-deoxyuridine (BrdU) to determine the hepatocyte labeling index. Livers were removed, weighed, and then immunostained. Morphological examination of the liver sections from all lobes was performed from control and 300 mg/kg group rats. 1,4-DCB treatment for 1 week did not produce morphological changes in the rat livers. 1,4-DCB produced significant dose-related increases in relative liver weight in the rats, which were also associated with mild centrilobular hypertrophy. At 300 mg/kg, relative liver weight was significantly increased. Significant dose-related increases in microsomal cytochrome P-450 content were observed in rats given 150 and 300 mg/kg 1,4-DCB for 1 week, with a significant dose-related induction of microsomal 7-pentoxyresorufin O-depentylase activity observed in rats given 75–300 mg/kg 1,4-DCB. The hepatocyte labeling index values were only increased in animals given 300 mg/kg 1,4-DCB (225% of controls) (Lake et al. 1997).

In a series of experiments, Eldridge et al. (1992) studied the acute hepatotoxic effects of 1,4-DCB and the role of cell proliferation in hepatotoxicity in $B6C3F_1$ mice and F344 rats. Mice and rats received a single dose of 1,4-DCB by gavage in corn oil of 600, 900, or 1,200 mg/kg/day. At 1, 2, 4, and 8 days after 1,4-DCB treatment, selected animals were injected intraperitoneally with BrdU 2 hours prior to sacrifice to monitor cell proliferation. Other groups of mice and rats were sacrificed 24 or 48 hours after dosing, blood was collected for liver enzyme analysis, and liver sections were collected for histopathology. In mice dosed with 600 mg/kg/day 1,4-DCB, liver weights were significantly increased 48 hours after dosing. Labeling index (LI), indicative of cell proliferation, peaked 24 hours after dosing in females and 48 hours in males. Activities of serum enzymes associated with liver damage (ALT, AST, LDH, sorbitol dehydrogenase) were not affected by 1,4-DCB. Twenty-four and 48 hours after administration of 1,4-DCB, the livers of males showed periportal hepatocytes with vacuolated cytoplasm and centrilobular hepatocytes with granulated basophilic cytoplasm; the severity of these changes was dose-related at 48 hours, but not at 24 hours. Similar but less pronounced effects were seen in females at 24 hours. In rats, liver weights were significantly increased at all time points after administration of 600 mg/kg/day 1,4-DCB. The LI peaked 24 hours after dosing and was still elevated after 48 hours. Necrosis was not observed in the livers of mice or rats after treatment with 1,4-DCB.

In pregnant CD rats administered 1,4-DCB in corn oil at doses of 250–1,000 mg/kg/day on Gd 6–15, no differences in maternal liver weight were noted (Giavini et al. 1986); however, hepatic effects have been reported in other oral studies in which 1,4-DCB has been administered to test animals by gavage (discussed below). These effects have ranged from temporary elevation of hepatic enzymes to hepatic degeneration and necrosis.

The effects of 1,4-DCB were compared in male $B6C3F_1$ mice given 0 (corn oil control), 300, and 600 mg/kg/day 1,4-DCB (n=6–8/group/time) by daily oral gavage 5 days/week for 1 week. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing BrdU to assess the hepatocyte labeling index. Livers were removed, weighed, and immunostained. Morphological examination of the liver sections was performed for control and 600 mg/kg groups. Biochemical analysis of liver whole homogenates was performed. 1,4-DCB produced significant dose-related increases in relative liver weight, which were associated with marked centrilobular hypertrophy. Relative liver weights were increased for mice in both the 300 and 600 mg/kg groups at all time points, with minimal centrilobular hypertrophy observed in 600 mg/kg group mice. No other histological abnormalities were observed in the liver sections. Administration of 1,4-DCB also produced a sustained induction of microsomal cytochrome P-450 content and 7-pentoxyresorufin O-depentylase activity. Significant dose-related induction of microsomal cytochrome P-450 content was induced in mice given 600 but not 300 mg/kg 1,4-DCB. Microsomal 7-pentoxyresorufin O-depentylase activity was significantly induced in mouse liver microsomes at doses of 300 and 600 mg/kg 1,4-DCB. Western immunoblotting studies demonstrated that 1,4-DCB induced CYP2B isoenzyme(s) in mouse liver microsomes at 300 and 600 mg/kg 1,4-DCB. The hepatocyte labeling index values were also significantly increased in mice given 300 and 600 mg/kg 1,4-DCB (Lake et al. 1997).

In male $B6C3F_1$ mice, single doses of 600, 1,000, or 1,800 mg/kg/day 1,4-DCB administered by gavage in corn oil resulted in significantly elevated BrdU labeling of hepatocytes at the 1,000 and 1,800 mg/kg/day doses. In addition, single doses of 1,800 mg/kg resulted in a 4.5-fold increase in serum ALT activity and severe centrilobular hepatocyte swelling. In a companion time-course study, single doses of 1,800 mg/kg 1,4-DCB administered by gavage in corn oil resulted in significantly elevated BrdU labeling in hepatic samples on days 2, 3, and 4, but not days 1 or 7. ALT activity was significantly elevated in 1,4-DCB-treated mice on day 2 only. In all other aspects, hepatic toxicity was not evident in mice dosed with 1,800 mg/kg 1,4-DCB (Umemura et al. 1996).

1,4-DCB has been shown to produce disturbances in porphyrin metabolism after high-level/acute-duration exposure. Increased excretion of porphyrins, especially coproporphyrin and uroporphyrin, are considered to be indicators of liver damage. Administration of 1,4-DCB in liquid paraffin to male rats at gradually increasing doses, until a dose level of 770 mg/kg/day was maintained for 5 days, resulted in high porphyrin excretion (Rimington and Ziegler 1963). Mean peak values of urinary coproporphyrin increased to about 10–15-fold above levels in controls. A 37–100-fold increase in urinary uroporphyrin levels occurred; porphobilinogen levels increased 200–530-fold; and a 10-fold increase in δ-aminolevulinic acid (δ-ALA) levels was observed. In the liver itself, coproporphyrin levels were similar to controls, uroporphyrin levels were increased 46-fold, and protoporphyrin levels were increased 6-fold. These dramatic increases, which suggest severe damage to the liver, were not observed when 1,4-DCB was administered to rats at higher levels (850 mg/kg/day) in 1% cellofas (Rimington and Ziegler 1963) or at lower levels for a longer period of time in another study (Carlson 1977), as discussed below. Also, Trieff et al. (1991) have used animal data on porphyrogenicity from various chlorinated benzenes to perform a QSAR study allowing prediction of ambient water criteria.

Changes in other markers of liver function including cytochrome P-450 levels, and activities of some drug-metabolizing enzymes (aminopyrine N-demethylase and aniline hydroxylase) were investigated in rats treated with of 1,4-DCB by gavage at 250 mg/kg/day for up to 3 days (Ariyoshi et al. 1975). Activity of δ-ALA synthetase, an enzyme used in synthesis of the heme moiety found in cytochromes, was increased 42% by treatment with 1,4-DCB. However, the cytochrome P-450 content did not change, although the microsomal protein content of liver preparations was increased. The toxicological significance of these findings is not clear since δ-ALA synthetase activity did not correlate with cytochrome P-450 concentration.

Effects on hepatic enzyme activities were reported to have occurred in adult male rats that were given 1,4-DCB by gavage for 14 days (Carlson and Tardiff 1976). Significant decreases in hexobarbital sleeping time and a 6.5-fold increase in serum isocitrate dehydrogenase activity were observed after a 14-day treatment regimen at 650 mg/kg/day. In addition, even at considerably lower levels (20 or 40 mg/kg/day), increases were observed in the activities of hepatic microsomal xenobiotic metabolic systems including levels of glucuronyl transferase, and benzpyrene hydroxylase and O-ethyl-O-nitro-phenyl phenylphosphorothionate (EPN) detoxification to nitrophenol. In a 90-day study at the same dosage levels, significant increases were seen in EPN detoxification, benzpyrene hydroxylase, and azoreductase levels. The former two levels were still elevated at 30 days after the cessation of administration of the compound. Most increases were noted at 20 mg/kg/day and above as in the 14-day

studies; however, azoreductase levels were elevated even at 10 mg/kg/day (Carlson and Tardiff 1976). These observations are important because they demonstrate that hepatic effects occur at levels of 1,4-DCB that are far below those associated with severe histopathology.

The effects of 1,4-DCB were compared in male F344 rats given 0 (corn oil control), 25, 75, 150, and 300 mg/kg/day 1,4-DCB (n=6–8/group/time) by daily oral gavage 5 days/week for 4 and 13 weeks. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing BrdU during study weeks 3–4 and 12–13. Livers were removed, weighed, and then immunostained. Morphological examination of the liver sections was performed from control and 300 mg/kg group rats in the 13-week exposure group. 1,4-DCB treatment produced a mild centrilobular hypertrophy seen in rats given 300 mg/kg 1,4-DCB for 13 weeks. No other histological abnormalities were observed in the liver sections. 1,4-DCB produced significant dose-related increases in relative liver weight in the rats, which were associated with mild centrilobular hypertrophy. At 300 mg/kg, relative liver weight was significantly increased. Significant increases in relative liver weight were observed in rats given 75 and 150 mg/kg 1,4-DCB for 4 weeks and 150 mg/kg 1,4-DCB for 13 weeks. Administration of 1,4-DCB also produced a sustained induction of microsomal cytochrome P-450 content and 7-pentoxyresorufin O-depentylase activity. Significant dose-related increases in microsomal cytochrome P-450 content were observed in rats given 25–300 mg/kg 1,4-DCB for 4 weeks and 75–300 mg/kg 1,4-DCB for 13 weeks. A significant dose-related induction of microsomal 7-pentoxyresorufin O-depentylase activity was observed in rats given 75–300 mg/kg 1,4-DCB for 4 weeks and 25–300 mg/kg 1,4-DCB for 13 weeks. Western immunoblotting studies demonstrated that 1,4-DCB induced CYP2B isoenzyme(s) in rat liver microsomes at 75 and 300 mg/kg 1,4-DCB (Lake et al. 1997).

Histopathological effects in the liver, including cloudy swelling and centrilobular necrosis, were observed after gavage administration of 1,4-DCB in rats (two per group) at 500 mg/kg/day for 4 weeks; similar results (cloudy swelling, focal caseous necrosis) were obtained in rabbits (five per group) given 92 doses of 1,000 mg/kg/day 1,4-DCB in olive oil over a 219-day period (Hollingsworth et al. 1956). The interpretation of this study is limited by the size of the test groups and the fact that observations in controls were not presented. Histopathological changes were also reported in a 13-week study in which rats received 1,4-DCB by gavage (NTP 1987). Doses of 1,200 or 1,500 mg/kg/day produced degeneration and necrosis of hepatocytes. Serum cholesterol levels were increased by doses of 600 mg/kg/day or more in male rats and by ≥900 mg/kg/day in female rats, while serum triglycerides and protein levels were reduced at doses of ≥300 mg/kg/day in male rats. Urinary porphyrins were increased in both sexes at ≥1,200 mg/kg/day. However, these increases were modest and considered by the authors

to indicate mild porphyrinuria rather than hepatic porphyria. Liver porphyrins were not increased at any dose. In a second 13-week study in the same laboratory, hepatic effects were not observed in rats at dosage levels up to 600 mg/kg/day (NTP 1987).

Similar hepatic effects were reported in two 13-week gavage studies in mice (NTP 1987). Hepatocellular degeneration was observed in both sexes at all doses (600–1,800 mg/kg/day). Serum cholesterol levels were increased in male mice at doses of 900 mg/kg/day or more, and serum protein and triglycerides were increased at doses of 1,500 mg/kg/day or more. These changes were thought by the authors to reflect the hepatic effects of this compound. Hepatic porphyria was not found in mice at any dose level in this study. Because hepatic effects were seen in mice in all dose groups in the first 13-week study, a second 13-week study was conducted at lower dosage levels. Hepatocellular cytomegaly was observed in mice at doses of 675 mg/kg/day and above. The lowest level at which hepatic effects were observed in mice was 600 mg/kg/day (in the first study).

Other intermediate-duration oral studies with 1,4-DCB have reported liver toxicity. In female rats dosed with 1,4-DCB by gavage for about 6 months, doses of 188 mg/kg/day and above resulted in increased liver weights. At 376 mg/kg/day, slight cirrhosis and focal necrosis of the liver were also observed (Hollingsworth et al. 1956). No effects on the liver were seen at a dose of 18.8 mg/kg/day.

The ability of 1,4-DCB to induce porphyria was investigated in female rats that were administered 1,4-DCB by gavage for up to 120 days (Carlson 1977). Slight but statistically significant increases in liver porphyrins were seen in all dosed rats (50–200 mg/kg/day) at 120 days. Urinary excretion of δ-ALA, porphobilinogen, or porphyrins was not increased over control levels. These results indicated that 1,4-DCB had only a slight potential for causing porphyria at these doses in female rats compared with the far more pronounced porphyrinogenic effects reported earlier in male rats that received 770 mg/kg/day for 5 days in a study by Rimington and Ziegler (1963). However, sex-related differences in susceptibility to 1,4-DCB's effects on these parameters cannot be ruled out in a comparison of these two studies.

The role of cell proliferation in liver toxicity induced by 1,4-DCB was examined in groups of mice (5–7 per sex per dose level) administered 0 (vehicle only), 300, or 600 mg/kg 1,4-DCB in corn oil by gavage 5 days/week for 13 weeks (Eldridge et al. 1992). The liver toxicity induced by 1,4-DCB was also examined in groups of female rats (5–7 per dose level) administered 0 (vehicle only) or 600 mg/kg 1,4-DCB in corn oil by gavage 5 days/week for 13 weeks. At various times during the study, mice were

implanted with osmotic pumps to deliver BrdU. Liver weights were significantly increased in high-dose male and female mice and in female rats throughout the 13-week study. Treated male mice showed a centrilobular pattern of labeled hepatocytes, whereas females were labeled throughout the lobules. At the lower-dose level, liver weight was increased in male and female mice at weeks 6 and 13. In a group of mice in which treatment with 600 mg/kg/day ceased after 5 weeks and the animals were allowed to recover for 1 week, liver weight returned to control values. The authors concluded that 1,4-DCB induced a mitogenic stimulation of cell proliferation in the liver rather than a regenerative response following cytotoxicity. This was evidenced by an increase in liver weight without increase in liver-associated plasma enzymes (Eldridge et al. 1992).

The effects of 1,4-DCB were determined in male $B6C3F_1$ mice given 0 (corn oil control), 300, and 600 mg/kg/day 1,4-DCB (n=6–8/group/time) by daily oral gavage 5 days/week for 4 and 13 weeks. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing BrdU during study weeks 3–4 and 12–13. Livers were removed, weighed, and immunostained. Morphological examination of the livers was performed for control and 600 mg/kg group mice at 13 weeks. Biochemical analysis of liver whole homogenates was also performed. 1,4-DCB produced significant dose-related increases in relative liver weight in the mice, which were associated with marked centrilobular hypertrophy. Relative liver weights were increased for mice in both the 300 and 600 mg/kg groups at all time points. At 13 weeks, a marked centrilobular hypertrophy was observed in the 600 mg/kg group. No other histological abnormalities were observed in the liver. Administration of 1,4-DCB also produced a sustained induction of microsomal cytochrome P-450 content and 7-pentoxyresorufin O-depentylase activity. Significant dose-related induction of microsomal cytochrome P-450 content was induced in mice given 600 but not 300 mg/kg 1,4-DCB for treatments of 4 and 13 weeks. Microsomal 7-pentoxyresorufin O-depentylase activity was significantly induced in mouse liver microsomes at doses of 300 and 600 mg/kg 1,4-DCB. Western immunoblotting studies demonstrated that 1,4-DCB induced CYP2B isoenzyme(s) in mouse liver microsomes at 300 and 600 mg/kg 1,4-DCB. Hepatocyte labeling index values were significantly increased in mice given 300 and 600 mg/kg 1,4-DCB for 4 weeks (420 and 395% of controls, respectively) (Lake et al. 1997).

A 1-year study in dogs indicates that this species is more sensitive than rats or mice to hepatic effects of 1,4-DCB. Groups of five male and five female Beagle dogs were administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996). Liver effects occurred after 6 and 12 months at ≥50 mg/kg/day in both sexes as shown by changes in liver enzymes, increased liver weight, and/or histopathology. Serum levels of ALT, AST, GGT, and AP were measured

after 6 and 12 months. Statistically significant increases were found for serum AP in males at 50 mg/kg/day, and females at 50 and 75 mg/kg/day, at months 6 and 12 (330–761% higher than controls); ALT in females at 75 mg/kg/day and month 12 (253% higher than controls); and GGT in females at 75 mg/kg/day and months 6 and 12 (131–161% higher than controls). Serum albumin was significantly decreased in males at ≥50 mg/kg/day (months 6 and 12) and females at 75 mg/kg/day (month 6). Absolute and relative liver weights were significantly increased in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatic lesions included hepatocellular hypertrophy in all males and females at 50 and 75 mg/kg/day (as well as one female at 10 mg/kg/day), hepatocellular pigment deposition at 50 and 75 mg/kg/day (two males and one female at each level), bile duct/ductule hyperplasia at 75 mg/kg/day (one male and one female), and hepatic portal inflammation at 50 and 75 mg/kg/day (periportal accumulation of neutrophils in an unspecified number of males). The 6- and 12-month increased serum AP levels in dogs (Naylor and Stout 1996) were used to derive intermediate- and chronic-duration oral MRLs of 0.07 mg/kg/day for 1,4-DCB.

Studies of the hepatic effects of chronic 1,4-DCB exposure are sparse. The toxicity of 1,4-DCB was evaluated in a group of seven rabbits administered 1,4-DCB in olive oil at a dose of 500 mg/kg/day a total of 263 times over a 367-day period. Slight changes in the liver (cloudy swelling and a few areas of focal caseous necrosis) were noted at sacrifice (Hollingsworth et al. 1956).

In the only study of lifetime oral exposure to 1,4-DCB in laboratory animals, groups of male and female F344 rats were administered 1,4-DCB by gavage in corn oil 5 days/week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females). Groups of male and female $B6C3F_1$ mice were administered 1,4-DCB at doses of 300 or 600 mg/kg/day by gavage in corn oil, 5 days/week for 103 weeks. No hepatic effects were seen in rats; in mice, the incidence of hepatocellular degeneration was greatly increased in treated mice (in males: 0/50 control, 36/49 low-dose, 39/50 high-dose; in females 0/50 control, 8/48 low-dose, 36/50 high-dose). The primary degenerative change was cellular swelling with clearing or vacuolation of the cytoplasm. Individual hepatocytes had pyknotic or karyorrhectic nuclei and condensed eosinic cytoplasm. Some necrotic hepatocytes formed globular eosinophilic masses in the sinusoids (NTP 1987).

Renal Effects.

1,2-Dichlorobenzene. No studies were located regarding renal effects in humans after oral exposure to 1,2-DCB.

A single 1,500 mg/kg gavage dose of 1,2-DCB in peanut oil (a lethal level) caused accumulation of albuminous fluid and casts in the renal tubules of rats (number and gender not reported) (DuPont 1982). Sprague-Dawley rats (10/sex/level) that were administered 1,2-DCB in corn oil by gavage in doses of 300 mg/kg/day for 10 consecutive days or 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991). In subchronic studies performed by NTP (1985), F344 rats and $B6C3F_1$ mice (10/sex/level/species) were administered 1,2-DCB in doses of 0, 30, 60, 125, 250, or 500 mg/kg/day in corn oil by gavage 5 days/week for 13 weeks. Histology examinations of the kidneys were limited to the 0 and ≥125 mg/kg/day dose groups in the rats and 0 and 500 mg/kg/day groups in the mice. Renal effects occurred only in the 500 mg/kg/day male rats; these included tubular degeneration (6/10 incidence compared to 0/10 in lower dose and control groups) and increased urine volume (57% higher than controls). There were no exposure-related increases in BUN in either species. In chronic studies performed by NTP (1985), there were no nonneoplastic tissue changes in the kidneys of male or female F344 rats (50/sex/level) exposed to 0, 60, or 120 mg/kg/day in corn oil by gavage for 5 days/week for 103weeks. In similarly-exposed $B6C3F_1$ mice (50/sex/level) exposure to 120 mg/kg/day, but not to 60 mg/kg/day, resulted in a significantly increased incidence of renal tubular regeneration (controls: 8/48; low dose: 12/50; high dose: 17/49) relative to controls. The incidence data for renal tubular regeneration in mice (NTP 1985) were used to derive a chronic-duration oral MRL of 0.3 mg/kg/day for 1,2-DCB. Renal end points other than histology were not assessed in the chronic studies.

1,3-Dichlorobenzene. No studies were located regarding renal effects in humans after oral exposure to 1,3-DCB.

No gross or histological changes were observed in the kidneys or urinary bladder in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995). Blood urea nitrogen (BUN) and kidney weight was measured in both studies, although only relative organ weights were reported. There was a statistically significant increase in relative kidney weight at ≥147 mg/kg/day in males and 735 mg/kg/day in females in the 90-day study, but this is not considered to be an adverse effect due to decreases in body weight gain and lack of changes in BUN and renal histology.

1,4-Dichlorobenzene. No studies were located regarding renal effects in humans after oral exposure to 1,4-DCB.

The role of cell proliferation in kidney toxicity induced by 1,4-DCB was examined in groups of male and female $B6C3F_1$ mice and F344 rats (Umemura et al. 1992). Mice were administered 300 or 600 mg/kg 1,4-DCB; in rats, males received 150 or 300 mg/kg 1,4-DCB while females received 300 or 600 mg/kg 1,4-DCB. All doses were administered by gavage in corn oil for 4 consecutive days. Cell proliferation was evaluated by means of immunohistochemical measurement of BrdU-labeled cells. In mice, kidney weights and cell proliferation in the kidney tubules were not altered by 1,4-DCB treatment; in rats, kidney weight was significantly increased in male rats at both dose levels, but was not affected in females. Cell proliferation was greatly increased in the proximal convoluted tubule from high-dose males. A lesser increase was seen in the proximal straight tubule from high-dose males; no increase was observed in the distal tubule from males or in any kidney region from treated female rats.

The effects of 1,4-DCB were compared in male F344 rats given 0 (corn oil control), 25, 75, 150, and 300 mg/kg/day 1,4-DCB (n=6–8/group/time) and male $B6C3F_1$ mice given 0 (corn oil control), 300, and 600 mg/kg/day 1,4-DCB (n=6–8/group/time) by daily oral gavage 5 days/week for 1 week. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing 5-bromo-2'-deoxyuridine during study weeks 0–1, 3–4, and 12–13. After sacrifice, the kidneys were removed, weighed, and immunostained. In rats, significant increases in relative kidney weight were observed in those rats administered 150 and 300 mg/kg 1,4-DCB for 4 and 13 weeks. 1,4-DCB treatment produced significant increases in rat renal P1/P2 proximal tubule cell labeling index values at all time points. Significant increases were seen in the following groups: 75 mg/kg 1,4-DCB at 4 weeks (250% of controls); 150 mg/kg 1,4-DCB at 4 and 13 weeks (400 and 440% of controls, respectively); and 300 mg/kg 1,4-DCB at 1, 4, and 13 weeks (170, 475, and 775% of controls, respectively). A significant increase in rat P3 renal proximal tubule cell labeling index values was observed in 300 mg/kg 1,4-DCB group rats at weeks 4 (185% of controls) and 13 (485% of controls). In contrast, some reduction in rat P3 renal proximal tubule cell labeling index values was observed in 75–300 mg/kg 1,4-DCB group rats at 1 week. In contrast, 1,4-DCB treatment produced little effect on mouse renal P1/P2 proximal tubule cell labeling index values at all time points tested. No significant increase was seen in 300 or 600 mg/kg 1,4-DCB groups for 1 and 13 weeks, but significant increases were seen at 4 weeks (205 and 170% of controls, respectively). Neither 300 nor 600 mg/kg 1,4-DCB for 1, 4, or 13 weeks had much effect on mouse P3 renal proximal tubule cell labeling index values (Lake et al. 1997).

In a study that examined the role of the protein $\alpha_{2\mu}$-globulin in 1,4-DCB-induced nephrotoxicity in male rats, NCI-Black-Reiter (NBR) rats, known not to synthesize the hepatic form of the $\alpha_{2\mu}$-globulin, were administered 500 mg/kg/day 1,4-DCB by gavage in corn oil for 4 consecutive days. Positive controls

consisted of F344 male rats treated with lindane; the results were also compared with those obtained in a group of female F344 rats treated with lindane. End points examined consisted of kidney lesions and protein droplet evaluation. $\alpha_{2\mu}$-Globulin was detected in kidney sections from male F344 rats, but not in male NBR or female F344 rats. No lesions or hyaline droplets were detected in treated or control male NBR and female F344 rats (Dietrich and Swenberg 1991).

Renal tubular degeneration has been observed in male but not female F344 rats in two 13-week gavage studies (NTP 1987). These effects were severe in male rats receiving ≥300 mg/kg/day in the first study, but in the second study, only slight changes were seen at 300 mg/kg/day, while moderate tubular degeneration was present at 600 mg/kg/day. Renal effects reported in another intermediate-duration gavage study in rats included increased renal weights at doses of ≥188 mg/kg/day (Hollingsworth et al. 1956). Renal effects were not observed in mice in either of two 13-week gavage studies using dosage regimens of 600–1,800 and 84.4–900 mg/kg/day (NTP 1987).

In a study designed to investigate the mechanism of renal toxicity for 1,4-DCB reported in the NTP (1987) studies, 1,4-DCB administered by gavage to male F344 rats at 7 daily doses of 120 or 300 mg/kg/day significantly increased the level of protein droplet formation in the kidneys of males but not females (Charbonneau et al. 1987). Administration of a single dose of ^{14}C-1,4-DCB by gavage at 500 mg/kg gave similar results. An analysis of the renal tissue of animals administered radio-labeled 1,4-DCB indicated that it was reversibly associated with the protein $\alpha_{2\mu}$-globulin. In a study designed to correspond to the experimental conditions of the 13-week NTP (1987) study in rats, 1,4-DCB was administered to F344 rats by gavage at 75–600 mg/kg/day for 13 weeks; interim sacrifices were performed at 4 weeks (Bomhard et al. 1988). At 4 weeks, females had no structural damage to the kidneys, while males experienced damage at the corticomedullary junction at doses of 150 mg/kg or more; damage consisted of dilated tubules with granular and crystalline structures, hyaline droplets, and desquamated epithelia. At all dose levels in the males, hyaline bodies were seen in the proximal tubule epithelial cells. At 13 weeks, males exhibited an increase urinary excretion of LDH and of epithelial cells over the entire dose range tested. These changes did not always appear to be dose-related. No signs of structural damage were seen in the females' kidneys. In males, a dose-dependent incidence of hyaline droplets in the cortical tubular epithelium was seen at 75 mg/kg/day and above. At ≥150 mg/kg/day, single-cell necrosis was observed, and at 300 and 600 mg/kg/day, epithelial desquamation of longer parts of the tubules were occasionally seen.

In the only available study of chronic-duration oral exposure to 1,4-DCB, renal effects were observed to occur preferentially in male rats. Male F344 rats exposed to 1,4-DCB at 150 and 300 mg/kg/day by gavage for 2 years exhibited the following effects with greater severity and in greater numbers: nephropathy, epithelial hyperplasia of the renal pelvis, mineralization of the collecting tubules in the renal medulla, and focal hyperplasia of renal tubular epithelium (NTP 1987). There was also increased incidence of nephropathy in female rats dosed with 1,4-DCB at 300 and 600 mg/kg/day, but there was minimal hyperplasia of the renal pelvis or tubules. Administration of 1,4-DCB at 300 and 600 mg/kg/day for 2 years also increased the incidence of nephropathy in male $B6C3F_1$ mice. Renal tubular degeneration was noted in female mice, but these changes occurred at a lower frequency and were qualitatively different from those in male rats (NTP 1987).

In a study with dogs, groups of five male and five female Beagles were administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996). Histopathological changes were observed in the kidneys that included collecting duct epithelial vacuolation in one male at 75 mg/kg/day, and in females at all dose levels (one at 10 mg/kg/day, one at 50 mg/kg/day, and two at 75 mg/kg/day). This renal lesion was considered to be a possible effect of treatment at ≥50 mg/kg/day where it was accompanied by increased relative kidney weight (50 mg/kg/day females) and gross observed renal discoloration (two females at 75 mg/kg/day). No gross or histological changes were found in the urinary bladder.

Endocrine Effects.

1,2-Dichlorobenzene. No studies were located regarding endocrine effects in humans after oral exposure to 1,2-DCB.

No gross or histological changes were observed in the adrenal or pancreas of Sprague-Dawley rats that were administered 1,2-DCB in corn oil by gavage in a dose of 300 mg/kg/day for 10 consecutive days, or in the adrenal (pancreas not examined) in rats similarly exposed to 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991). No gross or histological changes were observed in the adrenal, pancreas, thyroid, parathyroid, or pituitary of F344 rats or $B6C3F_1$ mice that were treated with 1,2-DCB in corn oil by gavage in doses ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding endocrine effects in humans after oral exposure to 1,3-DCB.

Gross and histological examinations of adrenals, pancreas, pituitary, thyroid, parathyroids, and gonads were performed in groups of 10 male and 10 female Sprague-Dawley rats that were exposed to 1,3-DCB in oil by daily gavage, in doses of 0 or 735 mg/kg/day for 10 consecutive days or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995). The 90-day study additionally included examinations of thyroid and pituitary at lower dose levels of 9, 37, and 147 mg/kg/day. No compound-related endocrine effects were observed in the 10-day study. As discussed below, the 90-day study found histological effects in the thyroid at ≥9 mg/kg/day and the pituitary at ≥147 mg/kg/day. The only other tissue with histological changes in the 90-day study was the liver (see Hepatic Effects).

Inflammatory and degenerative lesions in the McCauley et al. (1995) 90-day study were graded on a relative scale from one to four depending on severity (minimal, mild, moderate, or marked). In the thyroid, colloidal density in the follicular cells was significantly ($p \leq 0.05$) increased in male rats at ≥9 mg/kg/day and female rats at ≥37 mg/kg/day. The incidences of this lesion in the 0, 9, 37, 147, and 588 mg/kg/day dose groups were 2/10, 8/10, 10/10, 8/9, and 8/8 in males and 1/10, 5/10, 8/10, 8/10, and 8/9 in females. Depletion of colloid density in the thyroid was characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar. The severity of the colloid density depletion generally ranged from mild to moderate, increased with dose level, and was greater in males than females. For example, in the 147 and 588 mg/kg/day groups, severity was classified as moderate in males and mild for the females. Incidences of male rats with thyroid colloidal density depletion of moderate or marked severity were significantly increased at ≥147 mg/kg/day (0/10, 0/10, 2/10, 5/9, and 6/8). The lowest tested dose, 9 mg/kg/day, is considered to be a minimal LOAEL because the morphological alterations (reduced colloidal density in follicles) are unlikely to be associated with functional changes in the thyroid. The pituitary effect was cytoplasmic vacuolization in the *pars distalis* and only found in the male rats. Incidences of this lesion were significantly ($p \leq 0.05$) increased in males at ≥147 mg/kg/day (2/10, 6/10, 6/10, 10/10, and 7/7); incidences in the 9 and 37 mg/kg/day groups were marginally increased ($p=0.085$). The vacuoles were variably sized, irregularly shaped, and often poorly defined, and severity (number of cells containing vacuoles) ranged from minimal to mild. The severity of the lesions generally increased with increasing dose level, and incidences of male rats with pituitary cytoplasmic vacuolization of moderate or marked severity were significantly increased at 588 mg/kg/day (1/10, 0/10, 2/10, 3/9, and 7/7). The pituitary lesion was reported to be similar to “castration cells” found in gonadectomized rats, and considered to be an indicator of gonadal deficiency. No compound-related

pituitary lesions were observed in female rats. The incidences of pituitary lesions in male rats (McCauley et al. 1995) were used to derive an intermediate-duration oral MRL of 0.02 mg/kg/day for 1,3-DCB. Other effects in this 90-day study included significant increases in serum cholesterol in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day, and serum calcium in both sexes at ≥37 mg/kg/day. The study authors suggested that these serum chemistry changes might reflect a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs.

1,4-Dichlorobenzene. No studies were located regarding endocrine effects in humans after oral exposure to 1,4-DCB.

In a series of dose range-finding studies, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks. At sacrifice, animals were examined grossly and major tissues were examined histologically. No endocrine organs were affected in any of the 1,4-DCB-treated rats. In parallel studies with $B6C3F_1$ mice, no compound-related endocrine effects were observed after administration of 1,4-DCB at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987).

In the only study of lifetime oral exposure to 1,4-DCB in laboratory animals (NTP 1987), groups of male and female F344 rats were administered 1,4-DCB by gavage in corn oil, 5 days/week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females). Groups of male and female $B6C3F_1$ mice were administered 1,4-DCB at doses of 300 or 600 mg/kg/day by gavage in corn oil, 5 days/week for 103 weeks. In the F344 rats, an increased incidence of parathyroid hyperplasia was observed in males (4/42 controls, 13/42 low-dose, 20/38 high-dose), while no effect was seen in females. In mice, the incidence of thyroid follicular cell hyperplasia increased with dose in males (1/47 control, 4/48 low-dose, 10/47 high-dose), but not in females. The incidence of adrenal medullary hyperplasia and focal hyperplasia of the adrenal gland capsule also increased with dose in males (controls, 11/47; low-dose, 21/48; high-dose, 28/49).

No gross or histological changes were found in the adrenal, thyroid, parathyroid, pancreas, or pituitary glands of Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

Dermal Effects.

1,2-Dichlorobenzene. No studies were located regarding dermal effects in humans after oral exposure to 1,2-DCB.

No gross or histological changes were observed in the skin of Sprague-Dawley or F344 rats that were administered 1,2-DCB in corn oil by gavage in doses of 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985). Additionally, there were no gross or histological effects in the skin of $B6C3F_1$ mice that were similarly treated with ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985) or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding dermal effects in humans after oral exposure to 1,3-DCB.

No gross or histological changes were observed in the skin in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. A 19-year-old black woman who had been eating 4–5 moth pellets made of 1,4-DCB daily for 2.5 years developed symmetrical, well demarcated areas of increased pigmentation in a bizarre configuration over various parts of her body. After she discontinued this practice, the skin discolorations gradually disappeared over the next 4 months (Frank and Cohen 1961).

In laboratory animals, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks. No dermal effects were noted in any of the 1,4-DCB-treated rats. In parallel studies with $B6C3F_1$ mice, no compound-related dermal effects were observed after administration of 1,4-DCB at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987).

In the only study of lifetime oral exposure to 1,4-DCB in laboratory animals (NTP 1987), groups of male and female F344 rats were administered 1,4-DCB by gavage in corn oil, 5 days/week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females). Groups of male and female $B6C3F_1$ mice were administered 1,4-DCB at doses of 300 or 600 mg/kg/day by gavage in corn oil,

5 days/week for 103 weeks. No dermal effects have been reported in rats or mice at any of the studied doses.

No gross or histological changes were found in the skin of Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

Ocular Effects.

1,2-Dichlorobenzene. No studies were located regarding ocular effects in humans after oral exposure to 1,2-DCB. Opthalmoscopic examinations showed no effects in Sprague-Dawley rats that were dosed with 400 mg/kg/day of 1,2-DCB in corn oil by gavage for 90 consecutive days (Robinson et al. 1991). No gross or histological changes were observed in eyes of F344 rats or $B6C3F_1$ mice that were similarly exposed to ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985) or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding ocular effects in humans or animals after oral exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding the ocular effects in humans after oral exposure to 1,4-DCB.

In a series of intermediate-duration studies, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks. Ocular discharge was noted prior to death in males dosed with 1,200 mg/kg and in all rats exposed to 1,500 mg/kg. In parallel studies with $B6C3F_1$ mice, no compound-related ocular effects were observed after administration of 1,4-DCB at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days/week for 13 weeks (NTP 1987).

The ocular effects of oral administration of 1,4-DCB were examined in groups of white (strain not reported) female rats and male and female rabbits. Rats received 1,4-DCB in olive oil at doses of 18.8–376 mg/kg/day, 5 days/week for 192 days; rabbits received 1,4-DCB in olive oil at a dose of 1,000 mg/kg/day for 219 days. Under the study conditions, administration of 1,4-DCB did not produce cataracts in either species (Hollingsworth et al. 1956).

In chronic-duration toxicity studies in laboratory animals, Hollingsworth et al. (1956) found no evidence of cataract formation in rabbits administered a total of 263 doses of 500 mg/kg/day 1,4-DCB in olive oil over a 367-day period.

In two lifetime oral exposure studies (NTP 1987), groups of male and female F344 rats were administered 1,4-DCB by gavage in corn oil, 5 days/week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females); groups of male and female $B6C3F_1$ mice were administered 1,4-DCB at doses of 300 or 600 mg/kg/day by gavage in corn oil, 5 days/week for 103 weeks. In both species, no ocular effects were noted at any of the studied doses.

Opthalmoscopic examination showed no ocular effects in Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

Body Weight Effects.

1,2-Dichlorobenzene. No studies were located regarding body weight effects in humans after oral exposure to 1,2-DCB.

Gavage exposure to 1,2-DCB in oil has adversely affected body weight gain in rodent at doses that also caused other signs of toxicity. Decreases in body weight gain in the range of 10–20% were observed in rats exposed to 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991), 1,000 mg/kg/day for 14 consecutive days (NTP 1985), and 500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), as well as in mice exposed to 500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding body weight effects in humans after oral exposure to 1,3-DCB.

Body weight was measured in groups of 10 male and 10 female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by daily gavage, in doses of 0, 37, 147, 368, or 735 mg/kg/day for 10 consecutive days, or 9, 37, 147, or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995). Decreases in body weight gain occurred in both sexes at the high dose in both studies. In the 10-day study, final body

weights at 735 mg/kg/day were 20 and 13% lower than controls in males and females, respectively. The weight loss was progressive throughout the exposure period and, in males, accompanied by significantly reduced food consumption (12%, normalized by body weight). In the 90-day study, final body weights at 588 mg/kg/day were 24 and 10% lower than controls in males and females, respectively. The weight loss was progressive throughout the exposure period, and occurred despite increased food and water consumption.

1,4-Dichlorobenzene. No studies were located regarding body weight effects in humans after oral exposure to 1,4-DCB.

The effects of acute exposure to 1,4-DCB on body weight were examined in female Wistar rats given 1,4-DCB suspended in 2% tragacanth gum solution (a suspending agent obtained from the dried gummy exudation of *Astragalus gummifer*) at a dose of 250 mg/kg/day for 3 days. Under these conditions, no effects on body weight were seen (Ariyoshi et al. 1975). Male and female mice and female rats dosed once with 600 mg/kg/day 1,4-DCB also showed no discernible changes in body weight (Eldridge et al. 1992). Male rats administered 770 mg/kg/day of 1,4-DCB once a day for 5 days showed no changes in body weight (Rimington and Ziegler 1963). Pregnant CD rats that were administered 250–1,000 mg/kg/day 1,4-DCB in corn oil on Gd 6–15 experienced a reversible loss in maternal body weight (Giavini et al. 1986).

Body weight changes were observed in three studies in rats and mice (NTP 1987). In the first, both sexes of mice and female rats dosed at concentrations up to 1,000 mg/kg/day for 14 days by gavage demonstrated no changes in body weight during the test period. Male rats dosed at 500 mg/kg/day also showed no changes in body weight; however, a 7–12% decrease in body weight was noted in the 1,000 mg/kg/day dose group. In the second study (same route and duration as the first), male mice experienced a 13.3% decrease in body weight at the 250 mg/kg/day dose and a 14.7% decrease in body weight at the 2,000 mg/kg/day dose; however, results of intermediate doses demonstrated that there was no observable dose-response relationship for body weight changes. Neither male nor female rats dosed with 500 mg/kg/day showed any effects on body weights; however, a dose of 1,000 mg/kg/day resulted in a 13.5% decrease in weight for males and a 16.7% decrease in females. In the third study, male rats gavaged with 0, 25, 75, or 150 mg/kg of 1,4-DCB in corn oil for 7 days showed no changes in body weight; however, rats dosed at 300 mg/kg showed an approximately 10% decrease in body weight gain (Lake et al. 1997). The same study in male mice dosed with 0, 300, or 600 mg/kg of 1,4-DCB in corn oil for 7 days showed no changes in body weight at any dose level (Lake et al. 1997).

In intermediate-duration studies, no compound-related effects on weight gain were noted in albino or F344 rats administered 1,4-DCB by gavage in corn oil at doses up to 600 mg/kg/day, 7 days/week for 13 weeks (Bomhard et al. 1988; Carlson and Tardiff 1976). Male rats gavaged with 0 or 25 mg/kg of 1,4-DCB in corn oil for 7 days showed no changes in body weight; however, rats dosed at 75, 150, or 300 mg/kg showed an approximately 10% decrease in body weight gain (Lake et al. 1997). The same study in male mice dosed with 0, 300, or 600 mg/kg of 1,4-DCB in corn oil for 7 days showed no changes in body weight at any dose level (Lake et al. 1997). Male and female mice and female rats dosed with concentrations of 600 mg/kg/day 1,4-DCB 5 days/week for 13 weeks also showed no discernible changes in body weight (Eldridge et al. 1992). In a series of dose range-finding studies, groups of F344 rats were administered 1,4-DCB at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil, 5 days/week for 13 weeks (NTP 1987). In the first of these studies, there were no treatment-related effects on body weight at doses up to 600 mg/kg/day. In the second study, final body weight was decreased by 11% in low-dose males (300 mg/kg/day) relative to controls; in high-dose males (1,500 mg/kg/day), the reduction was 32%. The effect was less marked in females (6% reduction at 900 mg/kg/day; 11% reduction at 1,200 mg/kg/day). In parallel studies with $B6C3F_1$ mice, no compound-related effects on body weight were observed after administration of 1,4-DCB at concentrations up to 900 mg/kg/day; however, in the second study, final body weight was reduced in all males receiving 1,4-DCB (11.4% at 1,500 mg/kg/day to 13.9% at 600 mg/kg/day) and in females at 600 mg/kg/day (10.3%) (NTP 1987).

In two lifetime oral exposure studies, groups of male and female F344 rats and $B6C3F_1$ mice were administered 1,4-DCB by gavage in corn oil, 5 days/week for 103 weeks. Fischer 344 rats were administered 1,4-DCB at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females); mice were administered 1,4-DCB at doses of 300 or 600 mg/kg/day (NTP 1987). In mice, no effects on body weight attributable to treatment with 1,4-DCB were observed at doses up to 600 mg/kg/day. In rats, body weight gain was depressed by 12.5% in high-dose males (300 mg/kg/day) and by 12.4% in high-dose females (600 mg/kg/day) relative to vehicle controls.

There were no adverse body weight changes in Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

3.2.2.3 Immunological and Lymphoreticular Effects

1,2-Dichlorobenzene. No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to 1,2-DCB.

Immunological function has not been assessed in animals orally exposed to 1,2-DCB. No gross or histological changes were observed in the spleen, thymus, or lymph nodes of male or female Sprague-Dawley rats that were administered 1,2-DCB in corn oil by gavage in doses of 300 mg/kg/day for 10 consecutive days or 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991). Gross and histological examinations of lymph nodes, spleen, thymus, and bone marrow were performed in F344 rats and $B6C3F_1$ mice that were exposed to 1,2-DCB in corn oil by gavage 5 days/week in doses ≤500 mg/kg/day for 13 weeks or ≤120 mg/kg/day for 103 weeks (NTP 1985). The only changes in these tissues occurred at 500 mg/kg/day in the 13-week study; effects included lymphoid depletion in the thymus (4/10 male rats, 2/10 male mice, 2/10 female mice) and spleen (4/10 male mice, 2/10 female mice).

1,3-Dichlorobenzene. No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to 1,3-DCB.

Immunological function has not been assessed in animals orally exposed to 1,3-DCB. No gross or histological changes were observed in the spleen, thymus, or mandibular and mesenteric lymph nodes of male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days, or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995). Spleen and thymus weight was measured in both studies, although only relative organ weights were reported. In the 10-day study, relative spleen weight was significantly decreased in females at ≥368 mg/kg/day and males at 735 mg/kg/day, and relative thymus weight was significantly decreased in both sexes at 735 mg/kg/day. These changes are not considered adverse because body weight gain was decreased and they were not observed after 90 days or accompanied by histological alterations.

1,4-Dichlorobenzene. No studies were located regarding immunological effects in humans after oral exposure to 1,4-DCB. Symmetrical lesions with a bizarre pattern of skin pigmentation over most of her body were reported in the case study of a 19-year-old black woman who ingested 4–5 moth pellets of 1,4-DCB per day for a 2.5-year period (Frank and Cohen 1961). The lesion disappeared 4 months after

cessation. The described lesions may have been the result an immunological response to 1,4-DCB. However, this possibility was not addressed by the authors.

Groups of F344 rats were administered 1,4-DCB at concentrations ranging from 300 to 1,500 mg/kg/day by gavage in corn oil, 5 days/week for 13 weeks (NTP 1987). Treatment-related immunological and lymphoreticular effects noted in the study included hypoplasia of the bone marrow and lymphoid depletion of the spleen and thymus in males and females at doses of 1,200 mg/kg/day and above. In parallel studies with $B6C3F_1$ mice administered 1,4-DCB at concentrations ranging from 300 to 1,500 mg/kg/day, lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia of the spleen and bone marrow were noted in both males and females at doses of 1,500 mg/kg/day and above (NTP 1987).

Minimal lymphoreticular changes were noted in a chronic-duration study (NTP 1987). Male rats administered doses of 150 or 300 mg/kg/day and female rats given 300 or 600 mg/kg/day of 1,4-DCB by gavage 5 days/week for 2 years showed no discernible changes in the lymphoreticular system; however, mice dosed in a similar fashion and at a dose of 600 mg/kg/day showed an increased incidence of lymph node hyperplasia.

No gross or histological changes were found in spleen, thymus, or lymph nodes of Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

3.2.2.4 Neurological Effects

1,2-Dichlorobenzene. No studies were located regarding neurological effects in humans after oral exposure to 1,2-DCB.

Neurobehavioral function has not been assessed in animals orally exposed to 1,2-DCB. Ataxia and clonic contractions were observed in a small group of rats (three males) administered 1,2-DCB in liquid paraffin by gavage in a porphyrinogenic dose regimen of 455 mg/kg/day for 15 consecutive days (Rimington and Ziegler 1963). No clinical signs of neurotoxicity or histological changes in the brain were found in Sprague-Dawley or F344 rats that were administered 1,2-DCB in corn oil by gavage in doses of 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991), 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991), ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), or ≤120 mg/kg/day,

5 days/week for 103 weeks (NTP 1985). The 10-day rat study also found no histological changes in sciatic nerve tissue, and the 90-day rat study also found no changes in absolute or relative brain weight (Robinson et al. 1991). Additionally, there were no signs of neurotoxicity or histological effects in the brain of $B6C3F_1$ mice that were gavaged with ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985) or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding immunological effects in humans after oral exposure to 1,3-DCB.

Neurobehavioral function has not been assessed animals orally exposed to 1,3-DCB. No clinical signs of neurotoxicity, or histological changes in the nervous system (brain or sciatic nerve), occurred in male or female Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days, or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995).

1,4-Dichlorobenzene. Two case studies have reported neurological effects in humans exposed to 1,4-DCB via ingestion have been reported in two case studies. A 21-year-old pregnant woman developed pica (a craving for unnatural substances) for 1,4-DCB toilet bowl deodorizer blocks, which she consumed at the rate of 1–2/week throughout pregnancy (Campbell and Davidson 1970). Reported neurological effects included fatigue, dizziness, and mild anorexia. These effects, however, are common general symptoms that occur in many women during normal pregnancy. A 19-year-old black woman who ingested 4–5 pellets of 1,4-DCB daily for about 2.5 years developed tremors and unsteadiness after she stopped eating this chemical. However, in the opinion of the neurologist who evaluated the woman in this case report, the effects were considered to be psychological rather than the physiological effects of withdrawal from 1,4-DCB (Frank and Cohen 1961).

Two studies in laboratory animals indicate that oral exposure to 1,4-DCB may result in adverse neurological effects. In a study performed by Rimington and Ziegler (1963), three male albino rats were administered daily doses of 1,4-DCB in liquid paraffin at gradually increasing doses until a dose was reached (770 mg/kg/day), which resulted in high porphyrin excretion with very few fatalities; this dose was given for 5 days. Clinical symptoms associated with highly porphyric rats included extreme weakness, ataxia, clonic contractions, and slight tremors (a rarity). One rat receiving 1,4-DCB developed left-sided hemiparesis. In F344 rats administered 1,4-DCB by gavage in corn oil 5 days/week for 13 weeks, tremors and poor motor response were observed in males at 1,200 mg/kg/day and above, and in

both sexes at 1,500 mg/kg/day. However, administration of 1,4-DCB had no effect on brain weight or on the microscopical appearance of the brain, sciatic nerve, or spinal cord (NTP 1987).

In a chronic-duration study (NTP 1987), no neurological effects were noted either in rats dosed with 300 mg/kg/day of 1,4-DCB, 5 days/week for 2 years, or in mice dosed with 600 mg/kg/day, 5 days/week for 2 years.

No gross or histological changes were found in the brain, spinal cord (three levels), or peripheral or optic nerves of Beagle dogs (5/sex/level) that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

3.2.2.5 Reproductive Effects

1,2-Dichlorobenzene. No studies were located regarding reproductive effects in humans after oral exposure to 1,2-DCB.

Reproductive function has not been assessed in animals orally exposed to 1,2-DCB. No gross or histological changes were observed in the testes, seminal vesicles, prostate, or ovaries of Sprague-Dawley rats that were administered 1,2-DCB in corn oil by gavage in a dose of 300 mg/kg/day for 10 consecutive days (Robinson et al. 1991). There were no changes in testis or ovary weight (absolute or relative) or histology in Sprague-Dawley rats that were similarly exposed to 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991). Additionally, no gross or histological changes occurred in reproductive tissues of male (prostate, testes) or female (ovaries, uterus) F344 rats and B6C3F$_1$ mice that were similarly exposed to ≤500 mg/kg/day, 5 days/week for 13 weeks (NTP 1985) or ≤120 mg/kg/day, 5 days/week for 103 weeks (NTP 1985).

1,3-Dichlorobenzene. No studies were located regarding reproductive effects in humans after oral exposure to 1,3-DCB.

Reproductive function has not been assessed in animals orally exposed to 1,3-DCB. No histological changes occurred in male or female reproductive tissues (testes, seminal vesicles, prostate, preputial gland, clitoral gland, ovaries, or mammary gland).of Sprague-Dawley rats that were exposed to 1,3-DCB in corn oil by gavage in doses of 735 mg/kg/day for 10 consecutive days or 588 mg/kg/day for 90 consecutive days (McCauley et al. 1995). Testis and ovary weight was measured in both studies,

although only relative organ weights were reported. There was a statistically significant but small decrease (10.6% less than controls) in relative testes weight at 735 mg/kg/day in the 10-day study, but this is not considered to be an adverse effect because the magnitude of change was small, body weight gain was decreased, and there were no accompanying testicular histological alterations.

1,4-Dichlorobenzene. No studies were located regarding reproductive effects in humans after oral exposure to 1,4-DCB.

1,4-DCB was administered to female CD rats by gavage in corn oil on Gd 6–15 in a developmental toxicity study (Giavini et al. 1986). Doses up to 1,000 mg/kg/day had no adverse effect on the mean number of corpora lutea, mean number of implantations, mean percentage of pre- or postimplantation losses, or mean percentage of dams with resorptions (Giavini et al. 1986). In another developmental toxicity study of 1,4-DCB, female Wistar rats were exposed to a reported estimated dietary dose of 2 mg/kg/day from gestation day (Gd) 1 to postnatal day (Pnd) 21 for a total of 42 days (Makita 2005). There were no exposure-related effects on fertility, litter size, or sex ratio, and examinations of the pups at 6 weeks of age showed no changes in serum levels of reproductive hormones (leutinizing hormone [LH] and follicle stimulating hormone [FSH] in both sexes, testosterone in males) or weight or histology of reproductive tissues (testes, epididymides, prostate, seminal vesicles, ovaries, and uterus).

Intermediate- and chronic-duration toxicity studies were conducted in which F344/N and B6C3F$_1$ mice were treated with 1,4-DCB in corn oil by gavage 5 days/week (NTP 1987). No gross or histological changes were observed in reproductive tissues (testis, ovary, uterus, or mammary gland) of rats exposed to ≤1,500 mg/kg/day for 13 weeks or ≤300 mg/kg/day for 103 weeks, or mice exposed to ≤1,800 mg/kg/day for 13 weeks or ≤600 mg/kg/day for 103 weeks. No gross or histological changes were found in the testes, ovaries, or uterus of Beagle dogs that were administered 1,4-DCB by capsule in doses as high as 75 mg/kg/day, 5 days/week for 1 year (Naylor and Stout 1996).

In a 2-generation study, 1,4-DCB was administered by daily gavage in olive oil to male and female Sprague-Dawley rats at dose levels of 0, 30, 90, or 270 mg/kg/day (Bornatowicz et al. 1994). Groups of 24 F$_0$ rats/sex/ dose were treated for 77 days (males) and 14 days (females) before mating, followed by exposure of both sexes for 21 days during mating and females during gestation. Groups of 24 F$_1$ weanlings/sex/dose were treated for 84 days before mating, followed by exposure of both sexes for 30 days during mating and females during gestation (21 days) and lactation (21 days). There were no effects on mating or fertility in either generation as shown by duration between mating and successful

copulation, and fertility index (percentage of pregnant animals out of the number of inseminated animals). Additional reproductive indices were not evaluated as the emphasis of the study was on postnatal developmental toxicity. As discussed in Section 3.2.2.6, developmental effects included reduced birth weight in F_1 pups and increased F_2 pup deaths between birth and postnatal day 4 at ≥90 mg/kg/day.

3.2.2.6 Developmental Effects

1,2-Dichlorobenzene. No studies were located regarding developmental effects in humans after oral exposure to 1,2-DCB.

A limited amount of information is available on the prenatal developmental effects of 1,2-DCB in animals. In a gavage study inadequately reported as an abstract, Sprague-Dawley rats were administered 50, 100, or 200 mg/kg/day of 1,2-DCB on days 6–15 of gestation (Ruddick et al. 1983). Maternal end points included body weight gain, 15 unspecified biochemical parameters, and histology. Fetal toxicity was assessed by evaluating litter size, fetal weight, deciduoma, and skeletal, visceral, and histological changes. The maternal and fetal histological examinations included liver and thyroid; other tissues were not specified. No teratological effects or maternal toxicity were reported. Additional relevant information on the design and results of this study was not included in the abstract.

1,3-Dichlorobenzene. No studies were located regarding developmental effects in humans after oral exposure to 1,3-DCB.

The developmental toxicity study of 1,3-DCB is from a gavage study inadequately reported as an abstract (Ruddick et al. 1983). Sprague-Dawley rats were administered 50, 100, or 200 mg/kg/day of 1,2-DCB on days 6–15 of gestation (use of controls not specified). Maternal end points included body weight gain, 15 unspecified biochemical parameters, and histology. Fetal toxicity was assessed by evaluating litter size, fetal weight, deciduoma, and skeletal, visceral, and histological changes. The maternal and fetal histological examinations included liver and thyroid; other tissues were not specified. No teratological effects or maternal toxicity were reported. Additional relevant information on the design and results of this study was not included in the abstract.

1,4-Dichlorobenzene. No studies were located regarding developmental effects in humans after oral exposure to 1,4-DCB.

A dose-related increase in the incidence of an extra rib was observed in the fetuses of pregnant CD rats administered 1,4-DCB by gavage on Gd 6–15 at doses of 500, 750, and 1,000 mg/kg/day (Giavini et al. 1986). A reduction in fetal weight was observed at 1,000 mg/kg/day. The reduction in fetal weight was not considered to be a fetotoxic effect since it was associated with a decrease in maternal weight gain at the same dosage level. The structural anomaly observed in these fetuses was dose-dependant, but was not considered to be a true adverse effect by the authors. However, these results raise the question of whether 1,4-DCB ingested by the dams reached developing fetal tissue and elicited a developmental effect.

Additional information on prenatal developmental effects of orally administered 1,4-DCB is available from a gavage study inadequately reported as an abstract (Ruddick et al. 1983). Sprague-Dawley rats were administered 50, 100, or 200 mg/kg/day of 1,4-DCB on days 6–15 of gestation (use of controls not specified). Maternal end points included body weight gain, 15 unspecified biochemical parameters, and histology. Fetal toxicity was assessed by evaluating litter size, fetal weight, deciduoma, and skeletal, visceral, and histological changes. The maternal and fetal histological examinations included liver and thyroid; other tissues were not specified. No teratological effects or maternal toxicity were reported. Additional relevant information on the design and results of this study was not included in the abstract.

In a dietary study of 1,4-DCB, female Wistar rats were exposed to a reported estimated dose of 2 mg/kg/day from Gd 1 to Pnd 21 for a total of 42 days (Makita 2005). There were no maternal effects as shown by clinical signs or changes in body weight and food consumption. No fetal examinations were performed but perinatal evaluations showed no gross external malformations or effects on litter size, sex ratio, or pup viability on Pnd 1. Postnatal assessments of the offspring until 6 weeks of age showed no effects on body weight gain, anogenital distance, times of eye and vaginal opening and preputial separation, or serum levels of reproductive hormones (LH and FSH in both sexes and testosterone in males at 6 weeks). Examination of the liver, kidneys, spleen, thymus, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, and thymus at 6 weeks showed no effects on organ weight or histology, except for increased absolute thymus weight (approximately 20% higher than controls) in the female pups. The biological significance of this effect is unclear because it did not occur in the male offspring and was not accompanied by any histological changes.

A 2-generation study was conducted in which 1,4-DCB in olive oil was administered by daily gavage to male and female Sprague-Dawley rats at dose levels of 0, 30, 90, or 270 mg/kg/day (Bornatowicz et al. 1994). Groups of 24 F_0 rats/sex/dose were treated for 77 days (males) and 14 days (females) before mating, followed by exposure of both sexes for 21 days during mating and of females during gestation.

Exposure in the F_0 females was continued throughout lactation until weaning of the F_1 pups on postnatal day 21. Groups of 24 F_1 weanlings/sex/dose were treated for 84 days before mating, followed by exposure of both sexes for 30 days during mating, and of females during gestation and lactation. The study was ended following weaning of the F_2 pups on postnatal day 21. The F_0 and F_1 males were sacrificed 21 days after the end of the mating period (it is unclear if exposure continued postmating), and the F_0 and F_1 females were sacrificed after their pups were weaned. Study end points included clinical observations in adults and pups, body weight and food consumption in maternal animals (during gestation and lactation) and pups (from birth to day 21), reproductive indices, gestation length, litter size, numbers of live and dead pups, postnatal survival, postnatal developmental milestones (times to erect ears and eyelid separation), and neurobehavioral effects in pups at weaning (auricle reflex, orientation reaction, grasping, and draw-up reflexes). Necropsies were performed on all adult males and females, as well as on pups that died during the first 4 days or were killed on day 4 (i.e., those not selected for continuation in the study). Liver, kidney, and spleen weights were measured in males and females of both generations. Histopathological examinations were performed on selected tissues (liver, kidneys, spleen, vagina, cervix, uterus, ovaries, mammary gland, testes, epididymides, penis, prostate, seminal vesicles, and spermatic cord) from F_0 and F_1 adult animals that had no living young, died prematurely, or were killed as moribund, as well as on gross lesions in all animals.

There were no exposure-related effects in adult rats or pups at 30 mg/kg/day (Bornatowicz et al. 1994). Body weight was significantly reduced in F_1 pups at birth at ≥90 mg/kg/day (4.4, 5.7, and 22.6% lower than control group at 30, 90, and 270 mg/kg/day), in F_1 pups on postnatal days 7–21 at 270 mg/kg/day, and in F_2 pups at birth and on postnatal days 4–21. The total number of deaths from birth to postnatal day 4 was significantly increased in F_1 pups at 270 mg/kg/day and F_2 pups at ≥90 mg/kg/day (33, 467, and 1,033% higher than controls at 30, 90, and 270 mg/kg/day). None of the data in this study were reported on a per-litter basis or analyzed for dose-related trends. Decreased offspring survival at 270 mg/kg/day is also indicated by reduced total number of live F_1 and F_2 pups at birth, increased total dead F_1 and F_2 pups at birth, and increased total dead F_1 and F_2 pups during postnatal days 5–21. Other postnatal effects in the offspring included delayed eye opening (first day of appearance or day shown in all pups) in F_1 and F_2 pups at 270 mg/kg/day, delayed ear erection (day shown in all pups) in F_2 pups at 270 mg/kg/day, and reduced percentage of rats per litter with a positive draw-up reflex in the F_1 pups at 270 mg/kg/day and in F_2 pups at ≥90 mg/kg/day. Clinical manifestations occurred in pups of both generations at ≥90 mg/kg/day, including dry and scaly skin until approximately postnatal day 7 (0, 0, ≈70, and 100% of the litters at 0, 30, 90, and 270 mg/kg/day), and tail constriction that appeared between days 4 and 21 in all or nearly all litters (percentages not reported) and occasionally led to loss of parts of the tail.

Additionally, the number of F_1 pups described as cyanotic after birth was increased (not quantified) at 270 mg/kg/day.

Effects in adult animals were generally not quantified, but included reduced average body weight in F_1 males and females at 270 mg/kg/day at all time points during gestation and lactation, increased relative liver weight in F_1 males at ≥90 mg/kg/day, and changes in absolute and/or relative organ weights in kidneys (increased) and spleen (reduced) in F_1 males at 270 mg/kg/day. There were no effects on organ weights in female rats of either generation. The only histopathological finding attributed to exposure was unspecified kidney damage in both generations (effect levels, possible male specificity, and other information not reported). There were no effects on mating and fertility indices in any group (see Section 3.2.2.5).

3.2.2.7 Cancer

1,2-Dichlorobenzene. No studies were located regarding carcinogenic effects in humans after oral exposure to 1,2-DCB.

Carcinogenicity was evaluated in groups of 50 male and 50 female F344/N rats and 50 male and 50 female $B6C3F_1$ mice that were exposed to 1,2-DCB (>99% pure) in corn oil by gavage in doses of 0, 60, or 120 mg/kg, 5 days/week for 103 weeks (NTP 1985). Evaluations in both species included clinical signs, body weight, and necropsy and histology on all animals. As discussed below, no exposure-related tumors were found in either species, although it is unclear whether a maximum tolerated dose (MTD) was achieved in either species.

In rats, survival to termination in the high-dose males was significantly reduced compared with controls (19/50 vs. 42/50, $p<0.001$), but NTP (1985) concluded that the difference was likely mainly from causes incidental to treatment. Due to the probable gavage-related deaths in the high-dose male rats, the lower survival of this group does not necessarily mean that the MTD was either reached or exceeded. No clinical signs were reported. Mean body weight was slightly reduced (≈5% less than controls) in males throughout the study at 85.7 mg/kg/day; the only effect in females was a small increase compared to controls after week 32 in both dose groups (final body weights were 11–12% increased at 42.9 and 85.7 mg/kg/day). There were no exposure-related increased tumor incidences in the rats. The incidence of adrenal gland pheochromocytomas was significantly ($p\leq0.05$) increased in low-dose males by the life table test (mortality adjusted incidence of 20.9, 40.5, and 21.7% in the control, low-dose, and high-dose

groups, respectively), but not statistically significant by the incidental tumor test, which was considered to be the more appropriate mortality-adjusted test for analysis of nonfatal types of tumors. The increased incidence of pheochromocytomas in the low-dose males also was not significant in the Fisher Exact test (without mortality adjustment), and there was no significant dose-related trend in the Cochran-Armitage test. No increase in pheochromocytomas was seen in high-dose males. The increased incidence of pheochromocytomas in the low-dose male rats was discounted by NTP (1985) because there was no dose-response trend or high-dose effect, no increased incidence in females, no observation of malignant pheochromocytomas, and questionable toxicological significance of the life table test results (pheochromocytomas were not considered to be a life-threatening condition). Incidences of interstitial-cell tumors of the testis were elevated in control and treated groups (47/50, 49/50, 41/50), and occurred with a significant positive trend when analyzed by the life-table test. However, the increase detected by the life-table test was discounted by NTP because this tumor is not considered to be life threatening, and no significant results were obtained by the incidental tumor test, which is the more appropriate test for nonfatal tumors. The Cochran-Armitage test showed a significant negative trend for the interstitial cell tumors.

There were no clinical signs or effects on body weight or survival in the mice, indicating that it is unclear whether an MTD was achieved in this species (NTP 1985). There were no clear compound-related increased incidences of neoplasms in the mice. Incidences of malignant histiocytic lymphomas showed a significant positive dose-related trend in male mice (0/50, 1/50, 4/50) and female mice (0/49, 0/50, 3/49), but NTP considered numbers of animals with all types of lymphomas to be a more appropriate basis for comparison. Because malignant lymphocytic lymphomas occurred in male mice (7/50, 0/50, 0/50) with a significant negative dose-related trend, and the combined incidence of all types of lymphomas was not significantly different than that in controls for the male mice (8/50, 2/50, 4/50) or female mice (11/49, 11/50, 13/49) by any of the statistical tests, the increase in histiocytic lymphomas was discounted by NTP. Alveolar/bronchiolar carcinomas were significantly increased in the high dose male mice (4/50, 2/50, 10/50). The incidences showed a significant positive increasing trend by the Cochran-Armitage test, but not by the life-table or incidental tumor test. The increase in alveolar/bronchiolar carcinomas was discounted by NTP because the more appropriate combined incidence of male mice with alveolar/bronchiolar adenomas or carcinomas (8/50, 8/50, 13/50) was not significantly greater than controls in any of the tests.

1,3-Dichlorobenzene. No studies were located regarding carcinogenic effects in humans or animals after oral exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding carcinogenic effects in humans after oral exposure to 1,4-DCB.

1,4-DCB was found to be carcinogenic in $B6C3F_1$ mice and male (but not female) F344 rats exposed to 1,4-DCB for 2 years in a carcinogenesis bioassay (NTP 1987). 1,4-DCB was administered by gavage to male rats at doses of 150 or 300 mg/kg/day and female rats at doses of 300 or 600 mg/kg/day. Significant dose-related increases in the incidence of renal tubular cell adenocarcinomas were reported in male rats (controls, 2%; low-dose, 6%; high-dose, 14%). Spontaneous tumors of this type are uncommon in male F344 rats; they have been diagnosed in only 4 of 1,098 (0.4%) of the corn oil-gavage controls in previous NTP studies. There were no tubular cell tumors in dosed or vehicle-control female rats. There also was a marginal increase in the incidence of mononuclear cell leukemia in dosed male rats that was only slightly higher than the incidence in historical controls from the same laboratory. The NTP study concluded that 1,4-DCB was carcinogenic in male rats, but not in female rats.

In a 2-year bioassay in $B6C3F_1$ mice that received 1,4-DCB at 300 or 600 mg/kg/day (NTP 1987), increased incidences of hepatocellular carcinomas were observed in high-dose male mice (controls, 28%; low-dose, 22.5%; high-dose, 64%) and high-dose female mice (controls, 10%; low-dose, 10.4%; high-dose, 38%). Hepatocellular adenomas were increased in high- and low-dose male mice (controls, 10%; low-dose, 26.2%; high-dose, 32%) and in high-dose female mice (controls, 20%; low-dose, 12.5%; high-dose, 42%). Female control mice in this bioassay had a substantially higher incidence of liver tumors than did historical controls. Hepatoblastomas (a rare form of hepatocellular carcinoma) were observed in four high-dose male mice along with other hepatocellular carcinomas. This tumor type had not been previously observed in 1,091 male vehicle-control mice in NTP studies. An increase in thyroid gland follicular cell hyperplasia was observed in dosed male mice, and there was a marginal positive trend in the incidence of follicular cell adenomas of the thyroid gland in female mice. The incidence of pheochromocytomas (tumors of chromaffin tissue of the adrenal medulla or sympathetic pregangliar, benign and malignant, combined) of the adrenal gland was 0 of 47 (control), 2 of 48 (low dose), and 3 of 49 (high dose), and the incidence of adrenal gland medullary hyperplasia and focal hyperplasia of the adrenal gland capsule were increased as well in dosed male mice.

The observation that kidney tumors are induced in male rats, but not female rats, in response to exposure to certain chemicals has been the subject of recent research. It has been hypothesized that the male rat kidney is susceptible to the induction of certain tumors because it contains the protein $\alpha_{2\mu}$-globulin, which

has not been found at significant levels in either female rats, or in mice and humans of either sex (Charbonneau et al. 1987, 1989a, 1989b). Chemicals like 1,4-DCB, which reversibly bind to this protein, cause the formation of hyalin droplets in the proximal convoluted tubules of male rats. The hyalin droplet-protein complex is resistant to degradation by lysosomal enzymes and accumulates in the tubule, leading to localized hyperplasia of the epithelium (Borghoff et al. 1991; EPA 1991i). It is hypothesized that the resulting cellular damage and cell proliferation enhances tumor formation via a mechanism not yet elucidated. It has also been demonstrated that the same effects can be elicited in male rats administered other $\alpha_{2\mu}$-globulin-binding chemicals such as [hexachloroethane, d-limonene 1-methyl-4(1-methylethenyl)cyclohexene], unleaded gasoline, and pentachloroethane (EPA 1991i). Based on these data, EPA (1991) concluded that tumors associated with $\alpha_{2\mu}$-globulin and hyalin droplets are specific to species that produce this protein in large quantities, and that these tumors should be distinguished from other renal tumors.

The finding of hepatocellular carcinomas and adenomas in mice in the NTP (1987) study has been the subject of scientific debate. There was a high incidence of these tumors in both male and female control animals, but this is fairly common in mice. However, in this case, the tumor incidence in the female controls was substantially higher than the historical control value. In addition, 1,4-DCB has not been demonstrated to be mutagenic in any of the microbial or mammalian systems tested (NTP 1987), suggesting that the liver tumors are not the result of genotoxicity. Hepatocellular degeneration with resultant initiation of tissue repair was present in both male and female treated mice. This led NTP (1987) to speculate that 1,4-DCB acted as a tumor promotor rather than a tumor initiator during the formation of the liver tumors found in male and female mice.

As shown in Table 3-5, 300 mg/kg/day is the cancer effect level (CEL) for renal tubular cell adenomas in male rats and 600 mg/kg/day is the CEL for hepatocellular carcinomas and hepatoblastomas in mice (NTP 1987).

3.2.3 Dermal Exposure

3.2.3.1 Death

1,2-Dichlorobenzene. No studies were located regarding death in humans or animals after dermal exposure to 1,2-DCB.

1,3-Dichlorobenzene. No studies were located regarding death in humans or animals after dermal exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding death in humans after dermal exposure to 1,4-DCB.

The dermal LD_{50} for 1,4-DCB in Sherman rats was >6,000 mg/kg/day (Gaines and Linder 1986). It is not clear how many rats died after dermal exposure to 1,4-DCB in this study, and there are no toxicokinetic data that address the question of absorption of 1,4-DCB by the dermal route.

3.2.3.2 Systemic Effects

1,2-Dichlorobenzene. No studies were located regarding systemic toxicity in humans or animals after dermal exposure to 1,2-DCB.

Application of two drops of undiluted 1,2-DCB into the eyes of rabbits caused some pain and slight irritation of the conjunctival membranes, which healed completely within 1 week (Hollingsworth et al. 1958). The irritation was reduced by prompt rinsing with water. Additional relevant information was not reported.

1,3-Dichlorobenzene. No studies were located regarding systemic effects in humans or animals after dermal exposure to 1,3-DCB.

1,4-Dichlorobenzene. No studies were located regarding systemic effects in humans or animals after dermal exposure to 1,4-DCB.

Industrial experience indicates that solid particles of 1,4-DCB are painful in the eyes of humans (Hollingsworth et al. 1956). Solid 1,2-DCB has a negligible irritating action on intact, uncovered human skin, but can produce a burning sensation when held in close dermal contact for an unspecified excessive period of time (Hollingsworth et al. 1956). Prolonged and repeated contact to strong solutions of 1,4-DCB also could cause slight irritation in intact skin (Hollingsworth et al. 1956).

No studies were located regarding the following health effects in humans or animals after dermal exposure to 1,2-, 1,3-, or 1,4-DCB:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

In vivo and *in vitro* genotoxicity studies of DCBs are summarized in Tables 3-6 and 3-7, respectively.

1,2-Dichlorobenzene. No studies were located regarding genotoxic effects in humans after inhalation, oral, or dermal exposure to 1,2-DCB.

A limited amount of information is available on the genotoxicity of 1,2-DCB in animals. Micronuclei were induced in bone marrow erythrocytes of mice that were administered two 93.5–375 mg/kg doses by intraperitoneal injection 24 hours apart; lower dose levels were not tested (Mohtashamipur et al. 1987). A single 0.4 mg/kg intraperitoneal dose of 1,2-DCB caused covalent binding to liver, lung, kidney, and stomach DNA in rats and mice (Colacci et al. 1990).

In vitro reverse mutation assays of 1,2-DCB in microbial systems were negative in *Salmonella typhimurium* with or without metabolic activation (Connor et al. 1985; NTP 1985; Shimizu et al. 1983; Waters et al. 1982), negative in *Escherichia coli* without metabolic activation (Waters et al. 1982), and positive results in *Saccharomyces cerevisiae* with metabolic activation (Paolini et al. 1998). In mouse lymphoma cells, 1,2-DCB was negative for forward mutation without metabolic activation, but positive with S9 activation mixture (Myhr and Caspary 1991). *In vitro* exposure to 1,2-DCB induced DNA damage in *E. coli* and *S. cerevisiae*, but not in *Bacillus subtilis* (Waters et al. 1982), and did not cause replicative DNA synthesis in cultured human lymphocytes (Perocco et al. 1983) or increased DNA repair in primary rat hepatocytes (Williams et al. 1989). 1,2-DCB did not cause chromosomal aberrations, either with or without metabolic activation, in Chinese hamster ovary (CHO) cells, but did induce sister-chromatid exchanges only in the presence of S9 metabolic activation preparation (Loveday et al. 1990).

Table 3-6. Genotoxicity of Dichlorobenzenes In Vivo

Species (test system)	End point	Results	Reference
1,2-Dichlorobenzene			
Mammalian cells			
Mouse bone marrow erythrocytes[a]	Micronucleus formation	+	Mohtashampir et al. 1987
Rat liver, lung, kidney and stomach cells[b]	Covalent binding to DNA	+	Colacci et al. 1990
Mouse liver, lung, kidney and stomach cells[b]	Covalent binding to DNA	+	Colacci et al. 1990
1,3-Dichlorobenzene			
Mammalian cells			
Mouse bone marrow erythrocytes[c]	Micronucleus formation	+	Mohtashampir et al. 1987
1,4-Dichlorobenzene			
Mammalian cells			
Rat bone marrow cells[d]	Chromosomal aberrations	–	Anderson and Richardson 1976
Mouse bone marrow cells	Micronucleus formation	–	Shelby and Witt 1995
Mouse erythrocytes[e]	Micronucleus formation	–	NTP 1987
Rat kidney cells[f]	Unscheduled DNA synthesis	–	Steinmetz and Spanggord 1987b
	Increased DNA replication	+[g]	
Mouse hepatocytes[h]	Unscheduled DNA synthesis	–	Steinmetz and Spanggord 1987a
Rat kidney cells[i]	Increased DNA replication	+	Charbonneau et al. 1989b
Mouse bone marrow erythrocytes[j]	Micronucleus formation	+	Mohtashamipur et al. 1987
Rat renal tubular cells and hepatocytes[k]	Cumulative replicating fraction	–	Umemura et al. 1998
Mouse renal tubular cells and hepatocytes[k]	Cumulative replicating fraction	+	Umemura et al. 1998

[a]Exposed to 1,2-dichlorobenzene via two intraperitoneal injections of 93.5, 187.5, 281, or 375 mg/kg (24 hours apart) and sacrificed 6 hours after the second injection. Males only were tested.
[b]Exposed to 1,2-dichlorobenzene via one intraperitoneal injection of 0.4 mg/kg.
[c]Exposed to 1,3-dichlorobenzene via two intraperitoneal injections of 87.5, 175, 262.5, or 700 mg/kg (24 hours apart) and sacrificed 6 hours after the second injection. Males only were tested.
[d]Exposed to 1,4-dichlorobenzene via inhalation for 2 hours at 299 or 682 ppm; for 5 days, 5 hours/day at 75 or 500 ppm; or for 3 months, 5 days/week, 5 hours/day at 75 or 500 ppm.
[e]Exposed to 1,4-dichlorobenzene via gavage for 13 weeks, 5 days/week at 600–1,800 mg/kg/day.
[f]Exposed to 1,4-dichlorobenzene via gavage in corn oil at 300, 600, or 1,000 mg/kg at 16 hours before sacrifice for unscheduled DNA synthesis experiment or at 96 hours before sacrifice for DNA replication experiment.
[g]Results were positive for male rats only in which a significant S-phase response was induced.
[h]Exposed to 1,4-dichlorobenzene via gavage in corn oil at 300, 600, or 1,000 mg/kg at 16 or 48 hours before sacrifice.
[i]Exposed to 1,4-dichlorobenzene via gavage in corn oil at 120 or 300 mg/kg/day for 7 days and sacrificed 24 hours after the last dose.
[j]Exposed to 1,4-dichlorobenzene via two intraperitoneal injections of 355, 710, 1,065, or 1,420 mg/kg (24 hours apart) and sacrificed 6 hours after the second injection. Males only were tested.
[k]Exposed to 1,4-dichlorobenzene via gavage for 1 week or 4 weeks at 150, 300, or 600 mg/kg/day.

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

Table 3-7. Genotoxicity of Dichlorobenzenes In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
1,2-Dichlorobenzene				
Microbial systems				
Salmonella typhimurium TA98, TA100, TA1535, TA1537, and TA1538	Gene mutation	ND	–	Waters et al. 1982
S. typhimurium TA98, TA100, UTH8413, and UTH8414	Gene mutation	–	–	Connor et al. 1985
S. typhimurium TA98, TA100, TA1535, and TA1537	Gene mutation	–	–	NTP 1985
S. typhimurium TA98, TA100, TA1535, TA1537, and TA1538	Gene mutation	–	–	Shimizu et al. 1983
S. typhimurium	Gene induction (*umu*)	–	–	Nakamura et al. 1987
Escherichia coli	Prophage lambda induction			DeMarini and Brooks 1992
E. coli WP2 *uvra*	Gene mutation	ND	–	Waters et al. 1982
E. coli polA$^-$	DNA damage	ND	+	Waters et al. 1982
Bacillus subtilis recA$^-$	DNA damage	ND	+	Waters et al. 1982
Saccharomyces cerevisiae	Gene mutation	–	ND	Paolini et al. 1998
S. cerevisiae D3	DNA damage	ND	+	Waters et al. 1982
Mammalian cells				
Mouse lymphoma cells	Gene mutation	+	–	Myhr and Caspary 1991
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Loveday et al. 1990
Chinese hamster ovary cells	Sister-chromatid exchange	+	–	Loveday et al. 1990
Rat primary hepatocytes	Increased DNA repair	ND	–	Williams et al. 1989
Human lymphocytes	Replicative DNA synthesis	–	–	Perocco et al. 1983
1,3-Dichlorobenzene				
Microbial systems				
S. typhimurium TA98, TA100, TA1535, TA1537, and TA1538	Gene mutation	ND	–	Waters et al. 1982
S. typhimurium TA98, TA100, UTH8413, and UTH8414	Gene mutation	–	–	Connor et al. 1985

Table 3-7. Genotoxicity of Dichlorobenzenes In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
S. typhimurium TA98, TA100, TA1535, TA1537, and TA1538	Gene mutation	–	–	Shimizu et al. 1983
E. coli WP2 *uvra*	Gene mutation	ND	–	Waters et al. 1982
E. coli polA$^-$	DNA damage	ND	+	Waters et al. 1982
B. subtilis recA$^-$	DNA damage	ND	+	Waters et al. 1982
S. cerevisiae D3	DNA damage	ND	–	Waters et al. 1982
Mammalian cells				
Human lymphocytes	Replicative DNA synthesis	–	–	Perocco et al. 1983
1,4-Dichlorobenzene				
Microbial systems				
S. typhimurium[a] TA98, TA100, TA1535, and TA1538	Gene mutation	–	–	Anderson 1976
S. typhimurium[b] TA98, TA100, and TA1538	Gene mutation	–	–	Anderson 1976
S. typhimurium[b] TA1535	Gene mutation	+	–	Anderson 1976
S. typhimurium TA98, TA100, TA1535, TA1537, and TA1538	Gene mutation	–	–	Shimizu et al. 1983; Waters et al. 1982
S. typhimurium TA98, TA100, TA1535, and TA1537	Gene mutation	–	–	Haworth et al. 1983; NTP 1987
S. typhimurium TA98, TA100, UTH8413, and UTH8414	Gene mutation	–	–	Connor et al. 1985
E. coli WP2 *uvra*	Gene mutation	ND	–	Waters et al. 1982
E. coli polA$^-$	DNA damage	ND	-	Waters et al. 1982
B. subtilis recA$^-$	DNA damage	ND	-	Waters et al. 1982
S. cerevisiae	Gene mutation	+	ND	Paolini et al. 1998
S. cerevisiae D3	DNA damage	ND	-	Waters et al. 1982
Mammalian cells				
mouse lymphoma cells L5178Y/TK$^{\pm}$	Gene mutation	(=)	–	NTP 1987
mouse lymphoma cells L5178Y/TK$^{\pm}$	Gene mutation	+	(=)	McGregor et al. 1988
Chinese hamster lung cells	Gene mutation	–	–	Instituto di Ricerche Biomediche 1986b
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Anderson et al. 1990; NTP 1987

Table 3-7. Genotoxicity of Dichlorobenzenes In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Chinese hamster ovary cells	Sister chromatid exchanges	–	–	Anderson et al. 1990; NTP 1987
Rat hepatocytes	DNA fragmentation	ND	-	Canonero et al. 1997
Rat hepatocytes	Micronucleus formation	ND	(=)	Canonero et al. 1997
Rat kidney cells	DNA damage	ND	+	Robbiano et al. 1997
Rat kidney cells	Micronucleus formation	ND	+	Robbiano et al. 1997
Human kidney cells	DNA damage	ND	+	Robbiano et al. 1997
Human kidney cells	Micronucleus formation	ND	+	Robbiano et al. 1997
Human hepatocytes	DNA fragmentation	ND	-	Canonero et al. 1997
Human hepatocytes	Micronucleus formation	ND	-	Canonero et al. 1997
Human lymphocytes	Replicative DNA synthesis	–	–	Perocco et al. 1983
Human lymphocytes	Sister-chromatid exchanges	–	–	Carbonell et al. 1991
Human lymphocytes	Unscheduled DNA synthesis	–	–	Perocco et al. 1983; Instituto di Ricerche Biomediche 1987
HeLa cells	Unscheduled DNA synthesis	–	–	Instituto di Ricerche Biomediche 1986a
Plant systems				
Root tips (16 species of dicotyledons and monocotyledons)	Chromosomal aberrations	ND	+	Sharma and Battachary 1956
Lens esculenta (L.) Moench	Mitotic abnormalities	ND	+	Sarbhoy 1980
Aspergillus nidulans	Back mutation frequency	ND	+	Prasad 1970
Tribe viceae	Chromosomal aberrations	ND	+	Srivastava 1966

[a]Exposed to 1,4-dichlorobenzene gas.
[b]Exposed to 1,4-dichlorobenzene in DMSO.

– = negative result; + = positive result; (=) = equivocal; DNA = deoxyribonucleic acid; ND = not determined

1,3-Dichlorobenzene. No studies were located regarding genotoxic effects in humans after inhalation, oral, or dermal exposure to 1,3-DCB.

A limited amount of information is available on the genotoxicity of 1,3-DCB. Micronuclei were induced in bone marrow erythrocytes of mice following administration of two 87.5–700 mg/kg doses by intraperitoneal injection 24 hours apart; lower dose levels were not tested (Mohtashamipur et al. 1987). *In vitro* exposure to 1,3-DCB did not induce reverse mutations in *S. typhimurium* (Connor et al. 1985; Shimizu et al. 1983; Waters et al. 1982) or *E. coli* (Waters et al. 1982). 1,3-DCB caused DNA damage in *E. coli*, but not in *B. subtilis* or *S. cerevisiae* (Waters et al. 1982), and did not increase replicative DNA synthesis in cultured human lymphocytes (Perocco et al. 1983).

1,4-Dichlorobenzene. No studies were located regarding genotoxic effects in humans after inhalation, oral, or dermal exposure to 1,4-DCB.

Cytogenetic studies have been conducted using bone marrow cells of rats following inhalation exposure to 1,4-DCB (Anderson and Richardson 1976). Three series of exposures were carried out: (1) one exposure at 299 or 682 ppm for 2 hours; (2) exposures at 75 or 500 ppm, 5 hours/day for 5 days; and (3) exposures to 75 or 500 ppm, 5 hours/day, 5 days/week for 3 months. Bone marrow cells from both femurs were examined for chromosome or chromatid gaps, chromatid breaks, fragments, or other complex abnormalities. In all three experiments, exposure to 1,4-DCB failed to induce any effects indicative of chromosomal damage.

Gavage administration of 1,4-DCB to $B6C3F_1$ mice and F344 rats at single doses of 300–1,000 mg/kg/day did not result in unscheduled deoxyribonucleic acid (DNA) synthesis in the mouse hepatocytes or in the renal tissue of the rats in an *in vivo*/*in vitro* assay (Steinmetz and Spanggord 1987a, 1987b). However, 1,4-DCB at the highest level did induce an increase in DNA replication (S-phase of cell division) in the renal tissue of the male rats and in the hepatocytes of the male mice. Based on a comparison with historical controls, the authors concluded that levels of DNA replication were also significantly elevated in the hepatocytes of female mice.

No evidence of a clastogenic effect was found in mouse bone marrow erythroblasts after a single gavage administration of 1,4-DCB at 2,500 mg/kg/day (Herbold 1986a). Similarly, no evidence of clastogenic effects was found in mouse bone erythroblasts after a single oral administration of 2,5-dichlorophenol

(the major metabolite of 1,4-DCB) at 1,500 mg/kg/day (Herbold 1986b). 2,5-Dichlorophenol with or without metabolic activation did not induce an increase in mutagenic response in the Chinese hamster ovary HGPRT forward mutation assay (Litton Bionetics 1986a). This compound was also inactive in the Balb/3T3 *in vitro* transformation assay (Litton Bionetics 1985).

Cytogenetic effects were not found in bone marrow cells from mice treated with 1,4-DCB by gavage at levels up to 1,800 mg/kg/day in a 13-week study (NTP 1987). No increase in micronucleated cells occurred even at levels that were extremely toxic to the test animals, resulting in liver toxicity and decreased survival rates. As noted by the authors of that study, the observed carcinogenic activity of 1,4-DCB cannot be adequately predicted on the basis of the available genotoxicity data; all of the available information strongly suggests that 1,4-DCB acts as a tumor promoter rather than as a mutagen.

However, gavage administration of a single 1,000 mg/kg/day dose of 1,4-DCB to mice and rats resulted in an increase in DNA replication in the renal tissue of the male rats and in the hepatocytes of mice of both sexes (Steinmetz and Spanggord 1987a, 1987b). Increased ^{3}H-thymidine incorporation into renal DNA has also been demonstrated in rats dosed with 1,4-DCB by gavage at 120 mg/kg/day for 7 days (Charbonneau et al. 1989b). These observations suggest that 1,4-DCB promotes cell division, a finding that may help to elucidate the mechanism of carcinogenic action of 1,4-DCB in male rat kidneys and mouse liver in the NTP (1987) bioassay. However, it is important to note that in these studies; only kidney tissue was tested in the rat for increased DNA replication, and in the mouse, only liver tissue was tested. Therefore, it is not clear whether increased cell replication also occurs in other tissue in each species or is limited to the tissues in which the carcinogenic effects occurred.

The *in vivo* genotoxicity of 1,4-DCB is summarized in Table 3-6. As discussed above, the *in vivo* testing showed positive results for increased DNA replication in the livers of orally exposed mice (Steinmetz and Spanggord 1987a) and in the kidneys of orally exposed rats (Charbonneau et al. 1989b; Steinmetz and Spanggord 1987b), and mixed positive and negative findings for induction of micronuclei in bone marrow cells of orally exposed mice (Mohtashampir et al. 1987; NTP 1987).

In vitro genotoxicity studies of 1,4-DCB are summarized in Table 3-7. Microbial reverse mutation tests were predominantly negative in *S. typhimurium* (Anderson 1976; Connor et al. 1985; NTP 1987; Shimizu et al. 1983; Waters et al. 1982) and *E. coli* (Waters et al. 1982), but positive in *S. cerevisiae* (Paolini et al. 1998). Assays for DNA damage in *E. coli*, *B. subtilis*, and *S. cerevisiae* were negative (Waters et al. 1982). 1,4-DCB did not induce replicative DNA synthesis (Perocco et al. 1983) or DNA strand breaks

(Canonero et al. 1997) in rat and human hepatocytes, although DNA damage was increased in rat and human kidney cells (Robbiano et al. 1999). Forward mutation assays in mouse lymphoma cells were equivocal (McGregor et al. 1988; NTP 1987), and mixed positive and negative results were found for chromosomal aberrations and sister-chromatid exchanges in CHO cells (Anderson et al. 1990; Carbonell et al. 1991; NTP 1987). Tests for micronucleus formation were equivocal in human and rat hepatocytes (Canonero et al. 1997) and positive in human and rat kidney cells (Robbiano et al. 1999). *In vitro* testing in plant systems showed genotoxic effects that included chromosomal aberrations, mitotic abnormalities, and back mutations (Prasad 1970; Sarbhoy 1980; Sharma and Battacharya 1956; Srivastava 1966).

3.4 TOXICOKINETICS

1,2-DCB is quickly and extensively absorbed through both the gastrointestinal tract and the respiratory tract; studies describing the absorption of 1,2-DCB following dermal exposure are not available. Following absorption, 1,2-DCB is distributed throughout the body, but tends to be found in greatest levels in the fat, kidney, and liver. 1,2-DCB is initially metabolized by cytochrome P-450 enzymes, specifically P4502E1, to an active epoxide followed by hydrolysis to 2,3-dichlorophenol or 3,4-dichlorophenol. The dichlorophenols may be further oxidized or, more often, be conjugated to glutathione, sulfate, or to form the glucuronide; conjugation occurs extensively, with virtually no unconjugated metabolites reported in the available studies. Metabolism is believed to occur mainly in the liver, but may occur at lower levels in other tissues, such as the kidney or lung. Elimination of 1,2-DCB from the body is rapid, with the majority of a single dose being removed within the first 75 hours postexposure; elimination occurs primarily in the urine as metabolites.

Information on the quantitative absorption of 1,3-DCB in humans and animals is not available for any route of exposure; however, absorption of the compound can be inferred from studies that have detected 1,3-DCB or metabolites in the breast milk, blood, and fat of humans and in the bile and urine of exposed animals. Distribution is believed to be similar to the other DCB isomers, but data demonstrating this are not presently available. Similar to the other DCB isomers, 1,3-DCB is initially metabolized by cytochrome P-450 enzymes, followed by extensive conjugation, primarily to glutathione, has been reported. 1,3-DCB is eliminated mainly in the urine, similar to the other DCB isomers.

Absorption of 1,4-DCB is rapid and essentially complete following inhalation or oral exposure. Information on the quantitative absorption of 1,4-DCB following dermal exposure are not available; however, absorption is believed to be very low, based on a very high (>6 g/kg) dermal LD_{50} for 1,4-DCB

in rats, and on a lack of systemic effects in humans who held solid 1,4-DCB in their hands. Similar to the other dichlorobenzene isomers, 1,4-DCB is distributed throughout the body, but tends to be found in greatest levels in fat, liver, and kidney. Metabolism of 1,4-DCB is similar to that of 1,2-DCB, with an initial oxidation to an epoxide, followed by hydrolysis to 2,5-dichlorophenol. Extensive phase II metabolism occurs subsequently, with eliminated metabolites found mainly as the sulfate, glucuronide, or mercapturic acid. 1,4-DCB is eliminated almost exclusively in the urine, primarily as conjugates of 2,5-dichlorophenol.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

1,2-Dichlorobenzene. Quantitative data on the absorption of 1,2-DCB in humans following inhalation exposure are not available. However, evidence for absorption of 1,2-DCB in humans comes from numerous studies that have detected 1,2-DCB in human tissues, including the blood (Bristol et al. 1982), urine (Kumagai and Matsunaga 1995, 1997; Zenser et al. 1997), adipose tissue (Jan 1983), and in breast milk (Jan 1983; Mes et al. 1986). While these studies do not provide a quantitative measure of the rate or extent of 1,2-DCB and cannot provide information concerning possible exposure route, they provide evidence of 1,2-DCB absorption in humans.

Quantitative data on the absorption of 1,2-DCB in animals are similarly not available. However, numerous studies presenting evidence of systemic toxicity (see Section 3.2) following inhalation of 1,2-DCB provide qualitative evidence for the absorption of 1,2-DCB.

1,3-Dichlorobenzene. Quantitative data on the absorption of 1,3-DCB in humans following inhalation exposure are not available. However, evidence for absorption of 1,3-DCB in humans comes from studies that have detected 1,3-DCB in breast milk (Mes et al. 1986), blood (Bristol et al. 1982), and adipose tissue (Jan 1983). While these studies do not provide a quantitative measure of the rate or extent of 1,3-DCB and cannot provide information concerning possible exposure route, they provide evidence of 1,3-DCB absorption in humans.

Quantitative inhalation absorption data for 1,3-DCB are not available, but absorption characteristics are likely to be similar to those of the other isomers based on similarities in chemical and physical properties.

1,4-Dichlorobenzene. Quantitative data on the absorption of 1,4-DCB in humans following inhalation exposure are not available. However, evidence for absorption of 1,4-DCB in humans comes from numerous studies that have detected 1,4-DCB in human tissues, including the blood (Bristol et al. 1982; Hill et al. 1995), urine (Ghittori et al. 1985; Hill et al. 1995; Pagnotto and Walkley 1965), adipose tissue (Jan 1983), and breast milk (Jan 1983). While these studies do not provide a quantitative measure of the rate or extent of 1,4-DCB and cannot provide information concerning possible exposure route, they provide evidence that 1,4-DCB is absorbed by humans.

Studies presenting quantitative data on the rate and/or extent of absorption of 1,4-DCB following inhalation exposure in animals are not available. However, numerous studies presenting evidence of systemic toxicity (see Section 3.2) following inhalation exposure provide qualitative evidence for the absorption of 1,4-DCB. Additional evidence comes from studies that have reported the presence of the compound or its metabolites in peripheral tissues following inhalation exposure. Following a single or multiple 3-hour inhalation exposures of radiolabeled 1,4-DCB in rats, label was detected in all evaluated tissues (liver, kidneys, lungs, muscle, fat, and blood plasma), indicating that considerable absorption had occurred (Hawkins et al. 1980). Levels of label in tissues did not appreciably increase with increasing the number of exposures beyond one (Hawkins et al. 1980). Similarly, following a single 24-hour inhalation exposure in rats, 1,4-DCB levels in the liver, kidney, fat, and blood increased sharply during the first 6-hour evaluation period, then rose slowly but steadily for the remainder of the exposure period (Umemura et al. 1998), indicating an initial rapid absorption, followed by a slower total absorption as equilibration of body and blood levels is approached.

3.4.1.2 Oral Exposure

1,2-Dichlorobenzene. Quantitative data on the absorption of 1,2-DCB in humans following oral exposure are not available. However, absorption of 1,2-DCB in humans can be concluded based on the results of numerous studies that have detected 1,2-DCB in human tissues, including the blood (Bristol et al. 1982), urine (Kumagai and Matsunaga 1995, 1997; Zenser et al. 1997), and in breast milk (Jan 1983; Mes et al. 1986). While these studies do not provide a quantitative measure of the rate or extent of 1,2-DCB and cannot provide information concerning possible exposure route, they provide evidence of 1,2-DCB absorption in humans.

In male Wistar rats given single oral doses of 5, 50, and 250 mg/kg body weight of 14C-labeled 1,2-DCB, radioactivity in urine (collected for up to 175 hours after dosing) accounted for about 75, 84, and 75% of

the radioactivity for administered doses, respectively (Hissink et al. 1996a). Radioactivity in feces accounted for about 16, 12, and 7% of the respective administered doses. These results indicate absorption of at least 75–84% of the administered dose (assuming that none of fecal radioactivity was absorbed) occurred, and up to 82–96% of the dose (assuming that all radiolabel in the feces was first absorbed and later excreted in the bile) may have been absorbed. Rapid absorption was indicated since peak levels of radioactivity in blood samples occurred at about 6, 10, and 24 hours after administration of 5, 50, and 250 mg/kg doses, respectively (Hissink et al. 1996a). Other studies have identified the presence of metabolites of 1,2-DCB in the urine following oral exposure (Azouz et al. 1955; Hissink et al. 1996c).

1,3-Dichlorobenzene. Quantitative data on the absorption of 1,3-DCB in humans following oral exposure are not available. However, evidence for absorption of 1,3-DCB in humans comes from studies that have detected 1,3-DCB in breast milk (Mes et al. 1986), blood (Bristol et al. 1982), and adipose tissue (Jan 1983). While these studies do not provide a quantitative measure of the rate or extent of 1,3-DCB and cannot provide information concerning possible exposure route, they provide evidence of 1,3-DCB absorption in humans.

Evidence for absorption of 1,3-DCB following oral exposure of animals comes from the detection of metabolites in the urine and bile. Kimura et al. (1992) identified at least 12 metabolites in the bile of rats given 1,3-DCB by gavage, indicating that absorption and transport to the liver had occurred. In rabbits given oral 1,3-DCB, glucuronide, sulfur esters, mercapturic acid, and catechol metabolites were identified in the urine (Parke and Williams 1955), and suggested that 50–75% of the compound was absorbed, based on the presence of these metabolites.

1,4-Dichlorobenzene. Quantitative data on the absorption of 1,4-DCB in humans following oral exposure are not available. However, evidence for absorption of 1,4-DCB in humans comes from numerous studies that have detected 1,4-DCB in human tissues, including the blood (Bristol et al. 1982; Hill et al. 1995), urine (Hill et al. 1995; Ghittori et al. 1985; Pagnotto and Walkley 1965), adipose tissue (Jan 1983), and breast milk (Jan 1983). While these studies do not provide a quantitative measure of the rate or extent of 1,4-DCB and cannot provide information concerning possible exposure route, they provide evidence that 1,4-DCB is absorbed by humans.

Evidence for absorption of 1,4-DCB in animals includes studies demonstrating toxicity following oral exposure (see Section 3.2), as well as studies demonstrating the presence of 1,4-DCB or metabolites in

peripheral tissues following one or more oral exposures that indicate that 1,4-DCB is rapidly and nearly completely absorbed. Following a single or multiple oral exposures of radiolabeled 1,4-DCB in rats, label was detected in all evaluated tissues (liver, kidneys, lungs, muscle, fat, and blood plasma), indicating that considerable absorption had occurred (Hawkins et al. 1980). Additional support for a near-complete absorption comes from data showing that levels in tissues were similar following 10 oral exposures or 10 subcutaneous injections of 250 mg/kg. Levels of label in tissues did not appreciably increase with increasing the number of exposures beyond one (Hawkins et al. 1980). Similarly, Hissink et al. (1996b) reported that 70–85% of a single radiolabeled dose of 1,4-DCB was eliminated in the urine within 72 hours of exposure, indicating that 1,4-DCB was rapidly and extensively absorbed. By contrast, Klos and Dekant (1994) reported that ~41% of a labeled oral dose of 1,4-DCB was recovered in the urine 72 hours postexposure.

3.4.1.3 Dermal Exposure

1,2-Dichlorobenzene. Studies examining the absorption of 1,2-DCB in humans or animals following dermal exposure are not available.

1,3-Dichlorobenzene. Studies examining the absorption of 1,3-DCB in humans or animals following dermal exposure are not available.

1,4-Dichlorobenzene. No studies were located that specifically address the rate or amount of absorption of 1,4-DCB by humans or animals after dermal exposure to 1,4-DCB. Solid 1,4-DCB produces a burning sensation when held closely to the skin for an excessive period of time, but it does not produce irritation or systemic effects (Hollingsworth et al. 1956). In a study of the acute dermal toxicity of 1,4-DCB in adult Sherman rats, the dermal LD_{50} was estimated to be >6,000 mg/kg/day in both sexes (Gaines and Linder 1986). These data do not indicate that 1,4-DCB is absorbed to any extent after dermal exposure; dermal exposure to 1,4-DCB is associated with low systemic toxicity in both humans and laboratory animals.

3.4.2 Distribution

1,2-Dichlorobenzene. Quantitative data on the distribution of 1,2-DCB in humans are not available. 1,2-DCB has been detected in the blood (Bristol et al. 1982), urine (Kumagai and Matsunaga 1995, 1997; Zenser et al. 1997), and breast milk (Jan 1983; Mes et al. 1986) of humans.

The most comprehensive animal study of the distribution of 1,2-DCB following a single oral administration (10 mg/kg) is the study of Hissink et al. (1996a), which followed the distribution of the compound in exposed rats for up to 75 hours in 19 tissues, as well as the residual carcass and gastrointestinal tract. The results are presented in Table 3-8. 1,2-DCB was detected in all evaluated tissues, but at greatest concentrations in the urinary bladder, kidney, fat, and liver. Retention half-times ranged from 8.7 hours (urinary bladder) to 19.3 hours (brain), with only small levels of activity detectable in any tissue at 75 hours postexposure. In a separate study in the same manuscript, approximately 60% of an oral dose was found in the bile, indicating that considerable enterohepatic circulation occurs.

Twenty-two hours after a single intraperitoneal injection in Wistar rats or BALB/c mice, 1,2-DCB was found covalently bound to DNA, RNA, and proteins of liver, kidney, lung, and stomach (Colacci et al. 1990).

1,3-Dichlorobenzene. Quantitative data on the distribution of 1,3-DCB in humans are not available. However, 1,3-DCB has been detected in breast milk (Mes et al. 1986), blood (Bristol et al. 1982), and adipose tissue (Jan 1983), suggesting a wide distribution throughout the body.

Data are not available on the distribution of 1,3-DCB following inhalation exposure in animals. Kimura et al. (1983) reported the presence of 1,3-DCB or metabolites in the liver and kidney following oral exposure. Following oral exposure, 1,3-DCB undergoes enterohepatic circulation, as demonstrated by the data of Kimura et al. (1992), who identified at least 12 biliary metabolites in rats exposed to 1,3-DCB by gavage.

1,4-Dichlorobenzene. Quantitative data on the distribution of 1,4-DCB in humans are not available. However, 1,4-DCB has been detected in the blood (Bristol et al. 1982; Hill et al. 1995), urine (Hill et al. 1995; Ghittori et al. 1985; Pagnotto and Walkley 1965), adipose tissue (Jan 1983), and breast milk (Jan 1983) of humans, indicating distribution at least to those tissues.

Table 3-8. Tissue Concentrations (nmol/g tissue) of Radioactivity in Male Wistar Rats at Four Time Points after Oral Administration of 10 mg/kg ^{14}C-Labeled 1,2-Dichlorobenzene in Corn Oil

Tissue	6 hours	15 hours	30 hours	75 hours	$t_{1/2}$ (hours)
Liver	32.7±3.4	9.4±1.9	3.1±1.1	1.4±0.4	17.0
Kidney	132.5±107	15.7±4.8	3.8±0.7	1.5±0.4	13.1
Spleen	8.0±5.3	2.0±0.9	0.59±0.14	0.2±0.07	15.2
Pancreas	9.5±5.6	2.6±0.9	1.11±0.4	0.26±0.08	14.5
Lung	6.6±0.6	3.4±0.9	1.02±0.12	0.29±0.11	16.0
Heart	4.7±0.8	2.6±0.8	0.7±0.08	0.18±0.03	15.1
Brain	1.1±0.1	0.7±0.08	0.3±0.08	0.08±0.04	19.3
Skin	18.8±10.9	2.9±1.1	1.11±0.46	0.41±0.12	15.1
Femur	5.2±2.6	1.3±0.4	0.55±0.18	0.14±0.0	15.1
Skeletal muscle	4.7±3.1	1.3±0.6	0.45±0.2	0.09±0.04	13.5
Perirenal fat	33.4±12.1	14.0±2.6	2.18±0.3	0.18±0.03	9.4
Testis	3.6±0.8	1.9±0.4	1.13±0.9	0.2±0.07	17.2
Urinary bladder	183±121	17.3±13.6	6.6±6.4	0.32±0.04	8.7
Stomach	6.5±1.7	1.7±0.2	0.98±0.46	0.16±0.03	14.3
Small intestine	29.1±9.3	10.7±0.6	3.5±2.4	0.43±0.28	11.6
Caecum	16.4±4.8	16.7±1.1	2.8±2.2	0.27±0.07	11.1
Colon	7.5±2.2	12.0±2.4	1.4±0.9	0.20±0.07	12.0
Plasma	22.3±2.0	8.8±3.0	1.8±0.1	0.41±0.14	12.5
Red blood cells	9.2±1.0	3.4±0.6	1.6±0.4	0.57±0.22	18.8
Residual carcass	13±3%	4±2%	1±0.2%	0.3±0.07%	No data
Gastrointestinal tract contents	13±4%	15±4%	2±1%	0.1±0.04%	No data

Source: Hissink et al. 1996a

Studies in animals indicate that following absorption, 1,4-DCB is rapidly distributed throughout the body. Initially, 1,4-DCB accumulates in adipose tissue, but is not retained long-term. While distributed rapidly throughout the body, studies have demonstrated that very little of a dose of 1,4-DCB remains in tissues 72 hours postexposure (Hissink et al. 1996b; Klos and Dekant 1994; Umemura et al. 1998).

Following a single 24-hour inhalation exposure in rats, serum concentrations of 1,4-DCB rose sharply during the first 6 hours, then slowly for the next 18 hours. A sharp increase was seen in serum 1,4-DCB levels during the first 3 hours postexposure, which decreased rapidly thereafter. The greatest tissue concentrations of 1,4-DCB were found in the fat; concentrations in fat increased rapidly for the first 12 hours, then leveled off, remaining more or less steady until 6 hours postexposure, at which time they declined sharply (Umemura et al. 1990). Levels in the liver and kidney were approximately equivalent, although 10- to 20-fold lower than those in fatty tissues; in both liver and kidney, there was a steady increase in 1,4-DCB concentration for the 24 hours of exposure. In parallel with serum 1,4-DCB levels, there was a sharp, unexplained jump in the concentration of 1,4-DCB in both liver and kidney at 3 hours postexposure that resolved by 6 hours postexposure; concentrations fell rapidly thereafter. Following single or multiple inhalation exposures to radiolabeled 1,4-DCB, the greatest concentrations of label were found in the fat, with levels 10- to 20-fold greater than any other examined tissue (Hawkins et al. 1980). In nonfat tissues, the kidney showed the greatest amounts of label, on a per gram of tissue basis, followed by the liver, blood plasma, lungs, and muscle (Hawkins et al. 1980).

Following single or multiple oral exposures to radiolabeled 1,4-DCB, the greatest concentrations of label were found in the fat, with levels 6- to 15-fold greater than any other examined tissue (Hawkins et al. 1980). In nonfat tissues, the kidney showed the greatest amounts of label, on a per gram of tissue basis, followed by the liver, blood plasma, lungs, and muscle (Hawkins et al. 1980). Hissink et al. (1997a) reported that after a single oral dose of radiolabeled 1,4-DCB, a steady increase in radiolabel found in the blood, and in the plasma compartment, was seen for the first 8–10 hours, after which concentrations decreased steadily for the next 40 hours.

Within 12 hours after exposure of male rats to a single oral dose of 1,4-DCB, two sulfur-containing metabolites, 2,5-dichlorophenyl methyl sulfoxide, and 2,5-dichlorophenyl methyl sulfone (M2), were found in the blood, urine, fat, liver, and kidneys (Kimura et al. 1979). These metabolites remained in the blood after most of the 1,4-DCB had fallen below the detection limits of the assay. The maximum concentration of 2,5-dichlorophenyl methyl sulfoxide in blood was reached 15 hours after dosing and declined rapidly thereafter. For 2,5-dichlorophenyl methyl sulfone, two peaks were detected at 18 and

48 hours after dosing, which suggested to the authors that 2,5-dichlorophenyl methyl sulfone might undergo enterophepatic circulation. Changes in the levels of these metabolites in blood and tissues over a 120-hour period led the authors to suggest that 2,5-dichlorophenyl methyl sulfone might arise from 2,5-dichlorophenyl methyl sulfoxide.

3.4.3 Metabolism

Fisher et al. (1995) compared the metabolism and toxicity of the DCB isomers in liver slices prepared from human donor tissues, and from male Sprague-Dawley and F344 rats. At 2 and 6 hours, the metabolism of 1,4-DCB in human liver slices was similar to that seen in Sprague-Dawley and F344 rats. In human and F344 rat liver slices, the metabolism of 1,4-DCB was intermediate to that of 1,3- and 1,2-DCB at 2 hours; at 6 hours, the metabolism of 1,4-DCB was lower than that of 1,3- or 1,2-DCB. In Sprague-Dawley rats, the hepatic metabolism of 1,4-DCB was greater than that of 1,3- and 1,2-DCB at 2 hours, while at 6 hours, the metabolism of 1,4-DCB was intermediate to that of 1,3- or 1,2-DCB. In all three species, the metabolism of 1,4-DCB was not linear over time; the amount metabolized at 6 hours was only slightly higher than that metabolized after 2 hours. At both 2 and 6 hours, the amount of glucuronide and sulfate conjugates produced from 1,4-DCB was similar across all of the tested species.

1,2-Dichlorobenzene. The initial step in the metabolism of 1,2-DCB is metabolism by cytochrome P-450 isozymes, mainly P4502E1, to an active epoxide. This epoxide can either react directly with cellular components, be conjugated to glutathione or glucuronic acid, or be hydrolyzed to form 2,3-dichlorophenol or 3,4-dichlorophenol. The dichlorophenol metabolites can be further metabolized by conjugation with glutathione, glucuronic acid, or sulfate, or further oxidized to catechols. An additional oxidation to form dichlorohydroquinone metabolites has also been proposed.

Microsomal studies have implicated cytochrome P-450, and particularly P4502E1, as a major component of 1,2-DCB metabolism, resulting in the formation of dichlorophenols, dichlorocatechols, and dichlorohydroquinones. After exposure to 1,2-DCB in rat liver microsomes, dichlorohydroquinone metabolites>dichlorophenol metabolites>dichlorocatechol metabolites (den Besten et al. 1992). Increasing dose results in a greater formation of dichlorohydroquinone metabolites, with less dichlorophenol and dichlorocatechol metabolites, and a greater covalent binding to proteins. When 1,2-DCB was added to hepatic microsomes from animals treated with P-450 inducers, the major metabolites were dichlorophenols and dichlorohydroquinones (den Besten et al. 1992). 1,2-DCB in this system was also metabolized to a species that bound covalently with protein; addition of ascorbic acid

decreased the binding to protein by 68% (den Besten et al. 1992). Microsomes from rats and mice pretreated with benzene to induce cytochrome P-450 resulted in greater levels of metabolism of 1,2-DCB, both to soluble or covalently-bound products, than in untreated animals (Nedelcheva et al. 1998). Addition of diethyldithiocarbamate, a P-450 inhibitor, decreased 1,2-DCB metabolism by ≥90% in both normal and pretreated hepatic microsomes from rats and mice, and in normal human liver microsomes.

Addition of glutathione to the reaction mixture containing human or rat microsomes results in considerable (50–70%) formation of the glutathione-epoxide conjugate; addition of glutathione S-transferase enhances this proportion (Hissink et al. 1996c).

The metabolism of 1,2-DCB by isolated microsomes containing human cytochrome P-450 isozymes is accomplished mainly by cytochrome P4502E1 (Hissink et al. 1996a, 1996b). Incubation of 1,2-DCB with microsomes from cells expressing human cytochrome P-450 enzymes indicated that the 3,4-dichlorophenol was formed in greater amounts than the 2,3-dichlorophenol, and that in both cases, cytochrome P4502E1 was the most active isozyme (Bogaards et al. 1995).

Experiments using rat and human liver slices have detected the presence of sulfatase, glucuronide, and glutathione/cysteine conjugates following exposure to 1,2-DCB (Fisher et al. 1990, 1995). Covalent binding of 1,2-DCB metabolites to proteins has also been shown in experiments using rat and liver slices (Fisher et al. 1990, 1995).

Fisher et al. (1990) reported that in rat liver slices, the majority (>70%) of 1,2-DCB was found conjugated to glutathione, or as a cysteine conjugate, with only small amounts of the glucuronide or sulfate detected; only the conjugation status of the metabolite was reported. In human liver slices, the pattern was different, with approximately equal distribution of glucuronide and glutathione conjugates, and only minor amounts of the sulfate. Human liver slices metabolized approximately 50% more 1,2-DCB than did slices from F344 rats, and approximately 4-fold as much as slices from Sprague-Dawley rats (Fisher et al. 1995). Human liver slices formed 7–30-fold greater levels of glucuronide conjugates, 1.5–2-fold more sulphatase conjugates, and 1.5–2-fold more glutathione/cysteine conjugates of 1,2-DCB than rat liver slices (Fisher et al. 1995). Human fetal liver slices metabolized 1,2-DCB only about 10% as much as adult liver, and did so predominantly with conjugation to glutathione-S-transferase (GSH) (Fisher et al. 1990).

Azouz et al. (1955) identified urinary metabolites of 1,2-DCB in rabbits exposed to a single *in vivo* dose; 2,3- and 3,4-dichlorophenol were detected, as were considerable levels of glucuronide and sulfate conjugates; the presence of dihydroquinone metabolites was not reported. Pretreatment of F344 rats with inducers of cytochrome P-450 (phenobarbital, β-naphthoflavone, or pyridine) resulted in an increased toxicity of intraperitoneal 1,2-DCB while treatment with piperonyl butoxide, a P-450 inhibitor, reduced the toxicity of 1,2-DCB (Valentovic et al. 1993b). Evidence for binding of 1,2-DCB or its metabolites to glutathione includes the depletion of hepatic glutathione following a single intraperitoneal injection of 3.6 mmol/kg of 1,2-DCB in F344 or SD rats (Younis et al. 2000); depletion was nearly complete at 8 hours postinjection, and remained nearly complete at 12 hours postinjection. Fischer 344 rats recovered by 24 hours postinjection, but SD rats remained depleted.

Kumagai and Matsunaga (1995, 1997) reported that in occupationally-exposed humans, conjugated urinary metabolites of 1,2-DCB consisted of 3,4- and 4,5-dichlorocatechol and 2,3- and 3,4-dichlorophenol; there was a linear correlation between exposure concentration and the levels of these four metabolites in the urine.

1,3-Dichlorobenzene. Data on the metabolism of 1,3-DCB are less available than for the other two isomers of DCB. However, the available studies indicate that 1,3-DCB is metabolized by cytochrome P-450 to an epoxide and later to a dichlorophenol, followed by considerable secondary metabolism, similar to 1,2- and 1,4-DCB.

Fisher et al. (1990) reported that in rat liver slices, the majority (~70%) of 1,3-DCB was found conjugated to glutathione, or as a cysteine conjugate, with only small amounts of the glucuronide or sulfate detected. In human liver slices, the pattern was different, with approximately equal distribution (~40% each) of glucuronide and glutathione conjugates, and ~20% of the metabolites as the sulfate.

Human liver slices metabolized greater amounts of 1,3-DCB than did slices from F344 or Sprague-Dawley rats (Fisher et al. 1995). Human liver slices formed 2–9-fold greater levels of glucuronide conjugates, 1–4-fold greater levels of sulphatase conjugates, and 1–4-fold greater levels of glutathione/cysteine conjugates of 1,3-DCB than rat liver slices (Fisher et al. 1995).

Following *in vivo* exposure of rats to 1,3-DCB, the major sulfur-containing metabolites in the urine were 2,4- and 3,5-dichlorophenyl methyl sulfoxides and 3,5- and 2,4-dichlorophenyl methyl sulfones (Kimura et al. 1983). Kimura et al. (1992) identified 18 different biliary metabolites in rats exposed to a single

dose of 1,3-DCB; these were all heavily conjugated dichlorophenyl metabolites, with evidence of both mono- and diol formation, but no conjugated quinone derivatives.

Parke and Williams (1955) reported that following administration of 1,3-DCB to rabbits, the major urinary metabolites were 3,5-dichlorophenol and 2,4-dichlorophenol; the urine also contained 2,4-dichlrophenylmercapturic acid.

1,4-Dichlorobenzene. In general, the basic steps in metabolism of 1,4-DCB are similar to those of the other DCB isomers. The initial metabolic step is oxidation by cytochrome P-450, primarily P4502E1, to an epoxide and further to 2,5-dichlorophenol. The dichlorophenol may be further oxidized to dichlorocatechols, or possibly a dichlorohydroquinone, or may be conjugated by several phase II metabolism pathways. Support for the cytochrome P-450-mediated oxidation of 1,4-dichlorophenol, and subsequent conjugation reactions, comes from studies in isolated microsomes, liver slices, and exposures *in vivo*.

Analysis of the urine specimens of a 3-year-old boy who had been playing with 1,4-DCB yielded 2,5-dichlorophenol as well as four other unidentified phenols. These compounds were shown to be conjugated with glucuronic and sulfuric acids (Hallowell 1959).

After treatment of F344 rats with 1,4-DCB, the major biotransformation reaction is P-450-dependent oxidation to 2,5-dichlorophenol, which is then primarily conjugated to sulphate or glucuronic acid and eliminated in the urine (Hissink et al. 1996b; Klos and Dekant 1994); mercapturic acids were also identified in the urine of exposed rats. Following a single oral exposure of 1,4-DCB to male Wistar rats, the main sulfur-containing metabolites found in the urine were 2,5-dichlorophenyl methyl sulfoxide (M1) and 2,5-dichlorophenyl methyl sulfone (M2); levels of M2 in the blood were greater, and more persistant, following a single oral dose of 1,4-DCB (Kimura et al. 1979).

Hissink et al. (1997a) exposed male Wistar rats to 0, 10, 50, or 250 mg/kg of 1,4-DCB. Approximately 90% of the DCB was metabolized to the 2,5-dichlorophenol, which was detected in the urine as its sulfate (50–60%), glucuronide (20–30%), and the free form (5–10%); in the bile, the major metabolite was the glucuronide of 2,5-dichlorophenol. The remaining metabolites consisted of N-acetyl-cysteine-S-dihydro-hydroxy-1,4-DCB and N-acetyl-cysteine-S-1,4-DCB. No evidence for the formation of hydroquinones was seen, even under conditions of induced oxidative metabolism.

Following oral administration to Chinchilla rabbits, 1,4-DCB was also oxidized, principally to 2,5-dichlorophenol. A very high percentage of this metabolite was eliminated in the urine as conjugates of glucuronic or sulfuric acids (Azouz et al. 1955). Sulfur metabolites (methyl sulfides and methyl sulfones) of 2,5-dichlorophenol have been shown to induce cytochrome P450 activity (Kimura et al. 1983).

Fisher et al. (1990) reported that in rat liver slices, the majority (>60%) of 1,4-DCB was found conjugated to glutathione, or as a cysteine conjugate, with small amounts of the sulfate detected as well (~10% of total metabolites). In human liver slices, the pattern was different, with glutathione still being the predominant metabolite (~55%), but with an approximately equal distribution of glucuronide and sulfate conjugates (22–24%). In a later study, Fisher et al. (1995) reported that the total metabolism of 1,4-DCB was similar in liver slices from F344 rats, Sprague-Dawley rats, and humans. Human liver slices formed greater levels (~20–50%) of glucuronide conjugates of 1,4-DCB than rat liver slices; levels of formation of sulphatase and glutathione conjugates were similar in rats and humans (Fisher et al. 1995).

After a single exposure to 1,4-DCB in rat liver microsomes, dichlorohydroquinone metabolites were formed at greater levels than dichlorophenol metabolites, which in turn were more prevalent than dichlorocatechol metabolites (den Besten et al. 1992). Increasing the concentration does not change the percent formation of 2,5-dichlorohydroquinone, but decreases the formation of dichlorophenols in favor of increased covalent binding to proteins. Hissink et al. (1997b) reported that incubation of 1,4-DCB with microsomes of rat or mouse liver, in the presence of glutathione but lacking ascorbic acid or glutathione transferase enzymes, resulted primarily in the formation of S-glutathionyl-dichlorocatechol metabolites, 2,5-dichlorophenol, and 2,5-dichlorohydroquinone; rats appeared to be more efficient at forming a glutathione conjugate of the 2,3-epoxide than did mice, and formed less unconjugated 2,5-dichlorophenol and 2,5-dichlorhydroquinone.

Incubation of 1,4-DCB with microsomes from cells expressing human cytochrome P-450 enzymes indicated that the 2,5-dichlorophenol was the only isomer formed, and that cytochrome P4502E1 was the most active isozyme in its formation (Bogaards et al. 1995; Hissink et al. 1996a, 1996b). In human microsomes, metabolism of 1,4-DCB was lower than in rodents, with 2,5-dichlorophenol as the major metabolite, even in the presence of added GSH (Hissink et al. 1997b). Using cell lines expressing individual human cytochrome P-450 isozymes, it was revealed that CYP2E1, and not 1A1, 1A2, 2B6, 2C9, 2D6, 2A6, or 3A4, participated in 1,4-DCB metabolism.

Addition of diethyldithiocarbamate, a P-450 inhibitor, decreased 1,2-DCB metabolism by ≥90% in both normal or pretreated hepatic microsomes from rats and mice, and in normal human liver microsomes (Nedelcheva et al. 1998), providing additional evidence for the involvement of cytochrome P-450 in 1,4-DCB metabolism.

3.4.4 Elimination and Excretion

1,2-Dichlorobenzene. Following absorption, 1,2-DCB is eliminated primarily in the urine of both humans and animals, as metabolites rather than as the parent compound. Studies have detected the metabolites of 1,2-DCB in the urine of occupationally exposed humans (Kumagai and Matsunaga 1995, 1997; Zenser et al. 1997). While a linear correlation between airborne concentration and urinary metabolite levels has been demonstrated, a quantitative assessment of the percent urinary elimination has not been determined.

Quantitative data on elimination of 1,2-DCB comes from the study of Hissink et al. (1996a), which reported that following a single oral exposure to radiolabeled 1,2-DCB, 75–84% of the activity was detected in the urine 175 hours postexposure, with 7–16% being detected in the feces. Azouz et al. (1955) has also reported the elimination of 1,2-DCB and metabolites in the urine of exposed animals, although quantitative assessments of elimination were not presented.

1,3-Dichlorobenzene. Data on the elimination of 1,3-DCB in humans are not available.

Following a single dose of 1,3-DCB in rabbits, 50–75% of the compound was detected as urinary metabolites, indicating that the major route of elimination for 1,3-DCB is via the urine (Parke and Williams 1955). Kumura et al. (1984) also reported the presence of urinary metabolites of 1,3-DCB, although quantitative data were not presented. Additional data on the elimination of 1,3-DCB are not available.

1,4-Dichlorobenzene. Quantitative data on the elimination of 1,4-DCB in humans are not available. However, metabolites of 1,4-DCB have been detected in the urine of exposed humans (Ghittori et al. 1985; Hill et al. 1995; Pagnotto and Walkley 1965), demonstrating the urinary elimination of 1,4-DCB in humans.

Animal studies of 1,4-DCB elimination have demonstrated that the compound is eliminated mainly in the urine, regardless of exposure route; elimination occurs in the form of metabolites, rather than as the parent compound. Male Wistar rats given single oral doses of 10, 50, or 250 mg/kg of ^{14}C-1,4-DCB excreted the majority of 14C derived from 1,4-DCB in the urine as either the sulfate conjugate (60%) or the glucuronide (30%). Bile contained 5 and 30% of the total radioactivity after the low and high doses, respectively. Only minor amounts of mercapturic acid were found (Hissink et al. 1996b). In a later study, Hissink et al. (1997a) reported that following a single oral dose of 1,4-DCB in male Wistar rats, 75–85% of the dose was recovered in the urine, with only 2–5% being detected in the feces; clearance half-times did not vary with increasing dose level. Biliary excretion was dose-related, ranging from <5% at 10 mg/kg to 30% at 250 mg/kg (Hissink et al. 1997a). In male and female F344 rats administered a single dose of 900 mg/kg/day ^{14}C-1,4-DCB by gavage in corn oil, the excretion of radioactivity in the urine reached a peak in both males and females between 24 and 36 hours after dosing. Seventy-two hours after dosing, 41.3 and 3.6% of the dose was found in the urine and feces, respectively, of males; corresponding values in the urine and feces of females were 41.3 and 3.6% (Klos and Dekant 1994). Following oral or inhalation exposure in rats, levels of 1,4-DCB and its metabolites decreased only slightly over the first 8 hours postexposure in the liver, kidneys, fat, and plasma, but then fell rapidly and were nearly undetectable 120 hours after the final exposure (Hawkins et al. 1980). Elimination was primarily urinary, with 97% of the total recovered label found in the urine (Hawkins et al. 1980). Elimination in the expired air was negligible, being 1% of the total or less (Hawkins et al. 1980).

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and

Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

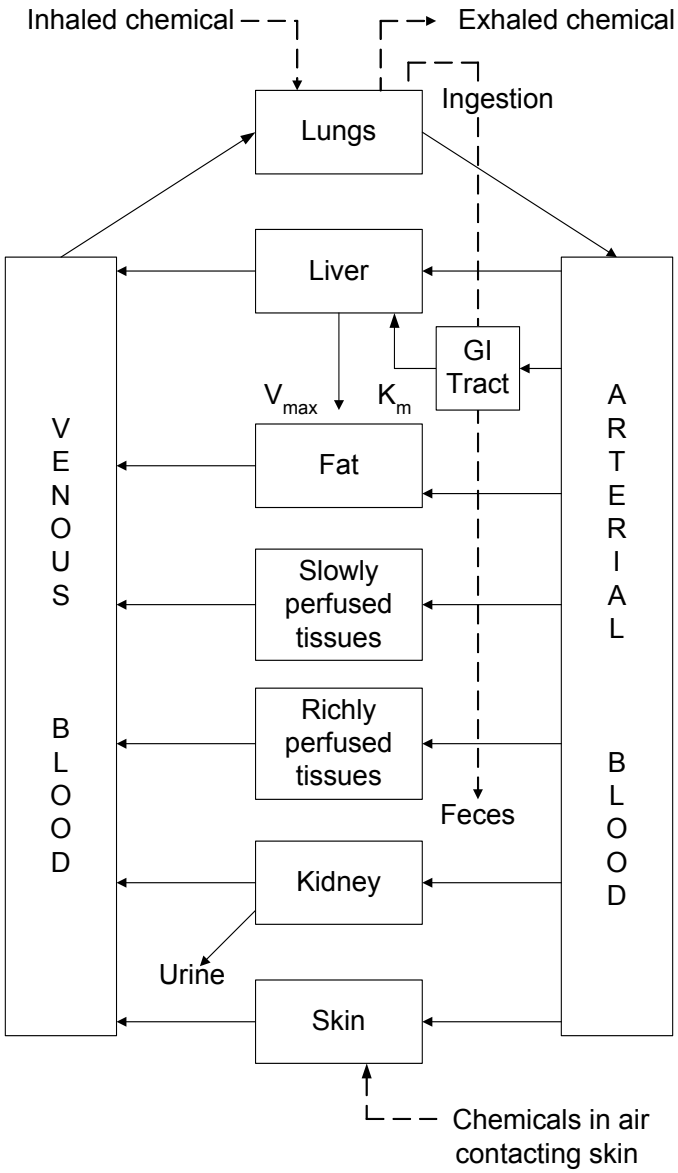
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-6 shows a conceptualized representation of a PBPK model.

If PBPK models for dichlorobenzenes 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.

Figure 3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

PBPK models are available for 1,2-DCB in rats and humans (Hissink et al. 1997b). No PBPK models have been developed for 1,3- or 1,4-DCB.

The rat and human PBPK models for 1,2-DCB were developed for oral exposure and do not include respiratory or dermal portals of entry (Hissink et al. 1997b). Both models have four compartments connected by blood flows: rapidly perfused tissues including the lung, kidneys, and spleen; slowly perfused tissues comprising muscle and skin; fat; and the liver, the only compartment in which metabolism is assumed to take place. The models assume that gastrointestinal tract uptake proceeds as a dose-dependent first-order kinetic process in which 1,2-DCB is deposited directly in the liver. For each of the nonmetabolizing compartments, differential equations describe the influx and efflux of 1,2-DCB. Equations are also used for the liver compartment to accounted for 1,2-DCB metabolism and reduced glutathione (GSH) synthesis, turnover, and consumption. Physiologic parameters, partition coefficients, biochemical parameters, and absorption rate constants used in the models are shown in Table 3-9. Absorption rate constants were estimated by fitting of the parameters to data for rats exposed to 5, 50, or 250 mg/kg 1,2-DCB.

Metabolism in the model is described as the initial, P-450-mediated, saturable formation of an epoxide, followed by epoxide transformation via three competing pathways that are assumed to independently follow pseudo first-order kinetics (i.e., are non-saturable): (1) conversion into dichlorophenol; (2) covalent binding to cellular macromolecules; and (3) conjugation with GSH. Michaelis-Menten constants, Vmax and Km, for the saturable cytochrome-P-450 oxidation of 1,2-DCB were initially estimated (in units of nmol/min-mg protein) from *in vitro* experiments with rat and human liver microsomes (Table 3-9). Scaling for use in the models assumed rat and human values of 45 and 77 mg microsomal protein/g liver, respectively. However, in order to obtain adequate fits to rat data for blood concentrations of parent material or total amount of metabolites, a "best-fit" Vmax value of 17 μmol/hour was used, along with the *in vitro* Km of 4.8 μM (Table 3-9). This "best-fit" value was about 4-fold higher than the rat *in vitro* Vmax scaled to units of μmol/hour (4.3 μmol/hour; see Table 3-9). Based on the rat data analysis, a factor of four was used to derive a "best-fit" Vmax value of 10,840 μmol/hour from the human *in vitro* Vmax (2,742 μmol/hour; see Table 3-9). The ratio of rate constants for the three epoxide-transforming pathways in rats (5:30:65) was estimated based on the relative amounts of *in vitro* covalent binding (5%), *in vitro* and *in vivo* dichlorophenol formation (25 and 30%), and *in vitro* and *in vivo* GSH conjugation (70 and 60%). For the rat model, the first-order rate constant for covalent binding was arbitrarily set at 50 $hour^{-1}$; the resultant constants for dichlorophenol formation and GSH conjugation

Table 3-9. Parameters in PBPK Models for 1,2-Dichlorobenzene

Parameter	Rat	Human
Physiologic parameters (as per Gargas et al. 1986)		
Body weight (kg)	0.258	70
Percentages of body weight		
Liver	4	3.14
Fat	7	23.1
Rapidly perfused	5	2.66
Slowly perfused	75	62.1
Flows (L/hour) [QC or QP= 15 L/hour (body weight)$^{0.74}$]		
Cardiac output (QC)	5.50	348.0
Alveolar ventilation (QP)	5.50	348.0
Percentages of cardiac output		
Liver	25	25
Fat	9	9
Rapidly perfused	51	51
Slowly perfused	15	15
Partition coefficients [calculated by methods of Droz et al. (1989) based on water:air, oil:air, and blood:air partition coefficients]		
Blood:air	423	423
Liver:blood	2.7	2.7
Fat:blood	66.4	66.4
Rapidly perfused:blood	2.7	2.7
Slowly perfused: blood	1.3	1.3
Biochemical parameters		
1,2-Dichlorobenzene oxidation		
Vmax (nmol/min-mg) (*in vitro* derived)	0.142 (4.3 μmol/hour)	0.27 (2,742 μmol/hour)
Km (μM) (*in vitro* derived)	4.8	7.5
Vmax (μmol/hour) ("best-fit" values)	17	10,840
GSH conjugation of epoxide (hour^{-1})	650	650
Formation of dichlorophenol (hour^{-1})	300	360
Formation of reactive metabolites (hour^{-1})	50	5
GSH turnover rate (hour^{-1})	0.14	0.14
Absorption rate constants (estimated by fitting parameters to data for rats at indicated dose levels)		
Ka (hour^{-1})		
5 mg/kg	0.5	No data
50 mg/kg	0.18	No data
250 mg/kg	0.06	0.06

Source: Hissink et al. 1997b

were 300 and 650 $hour^{-1}$, respectively (Table 3-9). *In vitro* data with human microsomes similarly formed the basis of the rate constants for these pathways: 5 $hour^{-1}$ for covalent binding, 360 $hour^{-1}$ for dichlorophenol formation, and 650 $hour^{-1}$ for GSH conjugation (Table 3-9). A GSH turnover rate of 0.14 $hour^{-1}$, determined in another study with rats (Potter and Tran 1993), was used in both the rat and human models (see Table 3-9).

The rat model was used to predict hepatic concentrations of covalently bound metabolites following an oral dose of 250 mg/kg 1,2-DCB that was expected to be toxic to the liver (Hissink et al. 1997b). The hepatic concentration in rats, 24 hours after dosing, was 1,459 μM. Versions of the human model using different Vmax values predicted that this administered dose level produced much lower hepatic concentrations of covalently bound metabolites in humans. Increasing the human *in vitro*-derived Vmax values by a factor of 10 did not increase the predicted human hepatic concentrations, 24 hours after dosing, to a value above about 240 μM. Therefore, the models predicted that equivalent administered doses in rats and humans would produce rat hepatic concentrations of covalently bound metabolites that are at least 6-fold higher in rats than humans.

The PBPK models were also used to predict hepatic concentrations of GSH (expressed as a percentage of an assumed baseline concentration of 6.5 mM) following an oral dose of 250 mg/kg 1,2-DCB (Hissink et al. 1997b). The rat model predicted that maximum depletion of GSH (about 70% depletion) occurred at 15 hours after dosing with 250 mg/kg. In contrast, the human model (using a Vmax value of 10,840 μmol/hour; see Table 3-9) predicted that maximum depletion of GSH (essentially 100% depletion) occurred at 10 hours after dosing. The models therefore predicted that humans may be more susceptible to 1,2-DCB depletion of hepatic GSH levels than are rats. Hissink et al. (1997b) noted that (1) if depletion of GSH is the only factor involved in acute 1,2-DCB hepatotoxicity, the models predict that humans may be more susceptible than rats at the same administered dose levels, and (2) if covalent binding of reactive metabolites is the critical factor, humans may be less susceptible to 1,2-DCB acute hepatotoxicity than rats. However, at present, the majority of parameters of the human model are based on direct scaling from the rodent data, rather than having been calibrated and validated using human data. Because the predictive ability of the human model has not been established, its usefulness is unclear.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Quantitative inhalation, oral, or dermal absorption studies in humans are not available for 1,4-DCB. In the few studies available in laboratory animals, absorption was demonstrated to occur during a 3-hour inhalation exposure to 1,000 ppm of 1,4-DCB (Hawkins et al. 1980) as evidenced by accumulation of ^{14}C in liver, kidney, plasma, and adipose tissue. No studies were located that described the absorption characteristics of 1,4-DCB after oral exposure; however, given the structural and physicochemical similarity to benzene, oral absorption is thought to be at or near 100% (EPA 1987a; Hawkins et al. 1980). A study assessing dermal absorption reported a dermal LD_{50} of >6,000 mg/kg/day in rats (Gaines and Linder 1986). Given the physicochemical properties, similarity to benzene, and lipid-soluble properties of 1,4-DCB, absorption by the inhalation, oral, and dermal routes of exposure is most likely by simple diffusion across cellular lipid membranes. No information is available that describes site-specific absorption within the respiratory tract (nasal epithelial absorption as opposed to alveolar absorption) or in the gastrointestinal tract.

Distribution. Quantitative inhalation, oral, or dermal distribution studies in humans are not available for 1,4-DCB. 1,4-DCB has been detected in human blood, adipose tissue, and breast milk after an assumed inhalation exposure in Tokyo residents (Morita and Ohi 1975; Morita et al. 1975), as well as people in some parts of the United States (EPA 1983b, 1986f). The available data indicate that after inhalation, oral, and subcutaneous exposure, 1,4-DCB preferentially distributes to the fat tissue and organ-specific sites within the body (Hawkins et al. 1980), following the order: adipose > kidney > liver > blood (Charbonneau et al. 1989b; Hawkins et al. 1980). Although 1,4-DCB is originally distributed primarily to adipose tissue, significant amounts of 1,4-DCB are not retained in that tissue after exposure ceases. Regardless of exposure route, most of the 1,4-DCB falls to near- or below-detectable assay limits in all tissues of the body except adipose tissues 48–72 hours after exposure, depending on the dose (Charbonneau et al. 1989b; Kimura et al. 1979). 1,4-DCB was detected in adipose tissue at 120 hours after exposure (Charbonneau et al. 1989b). In the kidney, 50% of the 1,4-DCB appears to localize within the cytosol in male F344 rats (Charbonneau et al. 1987). 1,4-DCB also does not appear to bind to tissue proteins (Klos and Dekant 1994).

Metabolism/Excretion. Quantitative inhalation, oral, or dermal metabolism and excretion studies in humans are not available for 1,4-DCB. One case study involving a 3-year-old boy who may have ingested 1,4-DCB reported the presence of 2,5-dichlorophenol in the urine (Hallowell 1959). Several

laboratory animal studies have indicated that 1,4-DCB is metabolized by phase I metabolism to 2,5-dichlorophenol (probably by cytochrome P-450), which then undergoes phase II metabolism/conjugation to the glucuronide or sulfate (Azouz et al. 1955; Hawkins et al. 1980; Hissink et al. 1996a; Kimura et al. 1979; Klos and Dekant 1994). Minor amounts of 2,4-dichlorohydroquinone may also be present (Klos and Dekant 1994). Metabolism occurs in the liver. None of the detected metabolites have been reported to be associated with the toxic effects seen with 1,4-DCB. Metabolites are excreted mostly in the urine (Azouz et al. 1955; Hissink et al. 1996a; Kimura et al. 1979); however, some metabolites (mainly the glucuronide conjugate) may also be excreted in the bile and feces (Hissink et al. 1996a). The role of enterohepatic circulation in the metabolism and excretion of metabolites is not completely known; however, it has been suggested that enterohepatic circulation may occur with some sulfated metabolites (Kimura et al. 1979). This phase I and II metabolic pathway mechanism (see below) seems plausible, in that other chemicals with similar (halogenated- and lipid-soluble) physicochemical properties undergo very similar metabolic routines to become more water-soluble and excreted. The data suggest that metabolism and excretion are similar in several species. It is likely that human metabolic pathways are similar, if not identical, to those established in laboratory animals.

3.5.2 Mechanisms of Toxicity

The precise mechanism of 1,4-DCB oxidation to 2,5-dichlorophenol has not thoroughly been investigated. 1,4-DCB is known to be metabolized by cytochrome P-450 (Azouz et al. 1955; Hawkins et al. 1980) in order to be presented to phase II metabolic pathways to increase its water solubility for excretion. A proposed metabolic pathway involving cytochrome P-450 with intermediate formations of metabolites has been outlined for 1,4-DCB (Den Besten et al. 1992). No information was available regarding specific or altered mechanisms of action for 1,4-DCB in children. The hepatotoxicity and nephrotoxicity observed in laboratory animals are likely due to the formation of toxic intermediates formed while converting 1,4-DCB to 2,5-dichlorophenol by cytochrome P-450, or by depletion of GSH at higher doses of 1,4-DCB, or both. Some indirect evidence of this was provided by Mizutani et al. (1994). In mice pretreated with DL-buthionine sulfoximine (BSO), a glutathione synthesis inhibitor, a single dose of 300 mg/kg 1,4-DCB caused significant elevations of ALT and liver calcium, both peaking between 24 and 32 hours after dosing and declining thereafter, indicative of hepatic damage. Necrotic changes were observed at those times as well as hemorrhage, fatty changes, and appearance of altered eosinophilic cells. A single 1,200 mg/kg dose of 1,4-DCB did not significantly alter ALT or liver calcium, but doses of 100 mg/kg or higher in mice pretreated with BSO produced dose-related alterations in these parameters. Increasing cellular GSH with GSH monoethyl ester protected the liver from the combination

of 1,4-DCB and BSO. In addition, pretreatment with microsomal cytochrome P-450-dependent monooxygenase inhibitors also protected the liver from the combined toxicity of 1,4-DCB and BSO. Pretreatment with the P-450 inducer beta-naphthoflavone did not significantly alter the effect of 1,4-DCB plus BSO. Pretreatment with phenobarbital partially blocked the effect of 1,4-DCB plus BSO on ALT and completely prevented the increase in liver calcium. PCBs prevented the effect on both ALT and liver calcium. Treatment with BSO alone or in combination with 1,4-DCB (300 mg/kg) greatly decreased hepatic GSH concentration, the effect being more pronounced with the combination. 1,4-DCB alone had no such effect. Depletion of GSH also has been reported to increase the toxicity of 1,4-DCB in rats (Stine et al. 1991). The data provide a strong indication that the mechanism behind the hepatic (and probably renal) toxicity of 1,4-DCB lies in the intermediate steps of metabolite formation and conjugation by cytochrome P-450. Formation of 2,5-dichlorophenol from 1,4-DCB via cytochrome P-450 metabolism likely produces some intracellular, intermediate metabolite(s) that are also hepatotoxic when sufficient amounts accumulate intracellularly. These yet unidentified metabolites are detoxified by GSH, but when GSH depletion occurs, which is likely to occur at higher oral doses, toxicity is enhanced. Hepatocytes respond to these insults by releasing intracellular enzymes (Carlson and Tardiff 1976; Umemura et al. 1996), degeneration, vacuolation (Eldridge et al. 1992; NTP 1987; Rimington and Ziegler 1963), necrosis, and increases in gross liver weight (Hollingsworth et al. 1956; Riley et al. 1980a). However, these changes are not specific to 1,4-DCB and likely occur in a dose-responsive manner. At lower doses, cellular proliferation in the liver in the absence of these toxic-type responses has been observed (Eldridge et al. 1992; Umemura et al. 1996); however, the mechanism behind this response needs to be more clearly defined. Exposure to 1,4-DCB likely follows similar metabolic pathways in the kidneys and would be responsible for the toxicity (increased organ weight, tubular degeneration, nephropathy) observed in that organ, and may also be linked to the known formation of cancer-linked $\alpha_{2\mu}$-globulin in male rats.

The metabolism of 1,4-DCB could involve the formation of an arene oxide intermediate, as has been proposed to occur in the oxidative metabolism of many halogenated aromatic hydrocarbons (Jerina and Daly 1974). 1,4-DCB has not been shown to be mutagenic in microbial or mammalian systems, a result that may be viewed as further suggestive evidence that an arene oxide intermediate is not involved in its metabolism.

1,4-DCB has also been reported to produce hematological effects associated with exposure in humans and laboratory animals. These findings have been limited to red and white blood cell anomalies (NTP 1987) in rats and mice, and may take place within the bone marrow at the time of red and white cell formation, although a precise and careful mechanism behind this finding has not been produced. Acute hemolytic

anemia and methemoglobinemia reportedly occurred in a 3-year-old boy who had played with, and possibly ingested, 1,4-DCB crystals (Hallowell 1959). A 21-year-old pregnant woman who had eaten 1–2 blocks of 1,4-DCB toilet air freshener per week throughout pregnancy developed severe microcytic, hypochromic anemia with excessive polychromasia and marginal nuclear hypersegmentation of the neutrophils. Heinz bodies were seen in a small number of the red cells. After she discontinued this practice (at about 38 weeks of gestation), her hemoglobin levels began to rise steadily. The mechanism behind these findings in the human exposures is unknown, but it appears that 1,4-DCB may have some local effect on the hemoglobin content of the red blood cell (hemolysis, methemoglobinemia, Heinz bodies). These are rare events in humans and only occur at very high exposure doses in laboratory animals. The clinical finding of Heinz-body formation in red blood cells and methemoglobinemia suggest that some form of oxidative stress is occurring to produce these findings, although the mechanisms behind these end points are not known. While there may not be any direct evidence, it is not unreasonable to suspect that oxidant metabolites of 1,4-DCB may inhibit glucose-6-phosphate dehydrogenase (G6PD), as do metabolites of aniline, leading to Heinz body production, methemoglobinemia, and hemolysis (Trieff et al. 1993). The effect on the red and white blood cell production processes in the bone marrow (anemia, polychromasia) is quite likely an effect related to blood loss associated with bleeding from esophageal varices which form secondary to liver cirrhosis.

3.5.3 Animal-to-Human Extrapolations

No studies were identified that specifically addressed the use of animal data applied to human exposure issues specifically related to 1,4-DCB. No physiologically based pharmacokinetic models are available to estimate risk associated with human exposure to 1,4-DCB. It is difficult to compare the toxicity of 1,4-DCB in laboratory animals to the toxicity observed in humans, since little reliable human data are available for examination (see Section 3.2). From the little data available, it appears that humans do have the potential to exhibit the same toxicological features of 1,4-DCB toxicosis as demonstrated or observed in the laboratory animal models studied. Although the mechanisms have not been outlined, human hematological responses (Campbell and Davidson 1970) and liver responses (Hallowell 1959) to 1,4-DCB have been similar to the responses of laboratory animals tested (Hollingsworth et al. 1956; NTP 1987). (However, the human hematological responses were vague and quite possibly unrelated.) Although the data are not sufficient to make direct comparisons, the possibility strongly exists that human responses may be similar to those of laboratory animals, and animal data should be taken into consideration until better human data become available. With the exception of the $\alpha_{2\mu}$-globulin observation in the male rat kidney (Bomhard et al. 1988), all of the detoxication pathways present in the

laboratory animal models are present in humans. This means that humans are likely to detoxify 1,4-DCB in a similar or identical manner to that of the laboratory animals, and suggests that humans are susceptible to the liver and possibly the renal lesions outlined for the laboratory animals studied (see Section 3.5.2). Due to the lack of acceptable dosing and exposure data in humans, it is not possible at present to definitively determine the magnitude of these human toxicological responses, the dose-response relationship, or whether humans are more or less susceptible to these effects on a mg/kg/day (oral and dermal) or ppm (inhalation) basis. It is also unknown whether the sex predilection found in male rats to 1,4-DCB renal or endocrine toxicity occurs in the human male.

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) and again by Colborn et al. (1993), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997c). 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).

Concern has been raised that many industrial chemicals, including DCBs, are endocrine-active compounds capable of having widespread effects on humans and wildlife (Colborn et al. 1993; Crisp et al. 1998; Daston et al. 1997; Safe and Zacharewski 1997; Versonnen et al. 2003). Particular attention has been paid to the possibility of these compounds mimicking or antagonizing the action of estrogen. Estrogen influences the growth, differentiation, and functioning of many target tissues, including female and male reproductive systems, such as mammary gland, uterus, vagina, ovary, testes, epididymis, and prostate. Most estrogenic chemicals have a ring structure included in the molecule, and *para*-substituted phenols generally bind better to the estrogen receptor and are more likely to exert xenoestrogenic effects than *ortho*- or *meta*-substituted compounds. In addition, there is evidence that some of these chemicals alter the thyroid hormone system, which is an important system for normal structural and functional development of sexual organs and the brain.

Insufficient information is available to adequately assess the endocrine disruptor potential of DCBs. Testing of 1,2-, 1,3-, and 1,4-DCB in the *in vitro* yeast estrogen screen (YES) assay showed that the 1,3- and 1,4- isomers were active in a concentration-responsive manner, although estrogenic potency was extremely weak (Versonnen et al. 2003). The relative potency relative to 17β-estradiol was 1.04×10^{-8} for 1,3-DCB and 2.2×10^{-7} for 1,4-DCB. The negative results for 1,2-DCB in this system are consistent with a lack of estrogenic activity of 1,2-DCB in *in vitro* yeast two-hybrid assays (Eguchi et al. 2003; Nishihara et al. 2000). The *in vivo* estrogenic activity of 1,2-, 1,3-, and 1,4-DCB was tested by measuring plasma vitellogenin (VTG) production in zebrafish (*Danio rerio*) that were exposed to each isomer for 14 days (Versonnen et al. 2003). VTG is a yolk protein precursor in teleosts and other oviparous vertebrates that is synthesized in response to estradiol stimulation. Elevated VTG levels were found in fish exposed to ≥10 mg/L of 1,4-DCB, but estrogenic potency was weak in comparison to ethynylestradiol, which increased VTG at ≥5 ng/L.

Histopathological changes occurred in the thyroid and pituitary glands of rats orally exposed to 1,3-DCB for 90 days (McCauley et al. 1995). Effects in the thyroid occurred at ≥9 mg/kg/day, the lowest tested dose, and included depletion of colloid density, characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar. Effects in the pituitary occurred at ≥147 mg/kg/day and included cytoplasmic vacuolization of the *pars distalis*. Increases in serum

cholesterol and serum calcium also occurred and were also believed to be related to effects on endocrine end points, possibly reflecting a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs. Histopathological changes in endocrine tissues were not observed in intermediate- and chronic-duration studies of 1,2-DCB (NTP 1985; Robinson et al. 1991) or 1,4-DCB (Aiso et al. 2005b; Japan Bioassay Research Center 1995; Naylor and Stout 1996; NTP 1987) in rats, mice, or dogs. Measurements of thyroid and other endocrine hormones have not been conducted in any study of DCBs.

Effects of 1,2- and 1,3-DCB on reproductive function have not been investigated. There were no effects on fertility or mating in 2-generation studies of 1,4-DCB in rats exposed orally to ≤270 mg/kg/day (Bornatowicz et al. 1994) or by inhalation to ≤211 ppm (Tyl and Neeper-Bradley 1989). No adverse histopathological changes in reproductive tissues were observed in intermediate- and chronic-duration oral studies of 1,2-DCB (NTP 1985; Robinson et al. 1991), 1,3-DCB (McCauley et al. 1995), and 1,4-DCB (Naylor and Stout 1996; NTP 1987).

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics

and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

There is little credible scientific information available on the susceptibility and toxicological effects of 1,4-DCB in children. The risk for exposure is apparently high. A study by Hill et al. (1995) measured blood levels of 1,4-DCB and urine levels of its metabolites in 1,000 adults, finding that exposure to 1,4-DCB was widespread, with 98% of the adults having measurable concentrations of 1,4-DCB metabolites in their urine. There is no evidence to indicate that children are likely to be exposed to lower amounts of 1,4-DCB from everyday living, suggesting that children are perhaps equally at risk for exposure and potential toxic side-effects.

Some information on possible health effects of DCBs in children is available from two case reports of 1,4-DCB exposure. Campbell and Davidson (1970) reported a case of a 21-year-old woman eating 1–2 toilet air-freshener blocks per week while pregnant. The mother developed hematological aberrations (hypochromic, microcytic anemia, polychromasia); however, she delivered an apparently normal female infant with no apparent hematological problems. Another report describes a 3-year-old boy who had been playing with crystals containing 1,4-DCB for 4–5 days before being admitted to the hospital. On admission, the boy was jaundiced, his mucous membranes were pale, and he was diagnosed with anemia and methemoglobinemia. After a blood transfusion, the child gradually improved, but it was unclear whether the boy actually ingested any of the 1,4-DCB (Hallowell 1959). These case reports are consistent with an expectation that health effects in children and adults are similar. Although there are no known differences in the toxicity of DCBs between adults and children, there is no evidence to substantiate the presumption.

Information on the reproductive toxicity of DCBs is essentially limited to a 2-generation oral study of 1,4-DCB in rats (Bornatowicz et al. 1994). There were no effects on mating or fertility in either generation, as assessed by a minimal number of end points (duration between mating and successful copulation and fertility index). The is a report of morphologically abnormal sperm in rats exposed to a high dose of 1,4-DCB by intraperitoneal injection (Murthy et al. 1987), but there are no studies that investigated transgenerational effects of exposure to DCBs.

Information on the developmental toxicity of 1,2-, 1,3-, and 1,4-DCB is available from oral and inhalation studies in rats and rabbits (Bio/dynamics 1989; Bornatowicz et al. 1994; Giavini et al. 1986; Hayes et al. 1985; Hodge et al. 1977; Ruddick et al. 1983; Tyl and Neeper-Bradley 1989). These studies provide no indications that DCBs are teratogenic, although fetotoxicity occurred at exposure levels that were also maternally toxic. A multigeneration study in rats that were orally exposed to 1,4-DCB found toxic effects in the pups during the nursing period, including increased neonatal mortality, dermal effects and other clinical manifestations, and reduced neurobehavioral performance (Bornatowicz et al. 1994). The postnatal developmental toxicity occurred at dose levels that were not maternally toxic and below those causing systemic toxicity in other animal studies. The results of this study indicate that postnatal developmental toxicity is the most sensitive end point in animals, and suggest a basis for potential concern in exposed children. Effects of DCBs on the immune and endocrine systems have not been adequately studied.

No studies are available that describe potential differences in the toxicokinetics or the mechanism of action of 1,4-DCB in children. No data are available that specifically describe whether 1,4-DCB or its major metabolites will cross the placenta; however, all three DCB isomers have been detected in placental tissues (Erickson et al. 1980; Pellizzari et al. 1982; Reichrtova et al. 1999). Because 1,4-DCB is not known to be genotoxic, it poses no threat to the DNA in parental germ cells. No PBPK models are available for children, fetuses/pregnant women, or infants/lactating women exposed to 1,4-DCB.

As discussed in Section 3.4, Toxicokinetics, the specific toxicokinetic behavior of 1,4-DCB in children (and immature laboratory animals) has not been reported. Based on its physicochemical properties, it is anticipated that the absorption, distribution, metabolism, and excretion of 1,4-DCB and its metabolites would be quite similar to that of the adult human (or animal), even when taking into account differences in body weight, total body water, body fat, volumes of distribution (V_D), and perhaps lower activities of some metabolizing enzymes (cytochrome P-450) during the natal and neonatal periods. 1,4-DCB is a lipid-soluble toxicant and is likely to pass across the placental membranes. It will likely accumulate in many of the same tissues in the fetus that it would normally be expected to accumulate in the adult, with the possible exception of fat storage in the fetus (Li et al. 1995). Some amount of 1,4-DCB accumulates in human breast milk (EPA 1983b), given its high lipid (milk fat) content, thereby providing a potential route of exposure to a nursing child, although there is no concrete data to support this relay exposure hypothesis. Some studies have noted that 1,4-DCB will preferentially distribute to adipose tissues in relatively high amounts, compared to accumulations in the liver and kidneys (Charbonneau et al. 1989b; Hawkins et al. 1980; Klos and Dekant 1994). Loss of maternal body fat may potentially mobilize 1,4-DCB from fat storage deposits in exposed mothers. This mobilization could result in increased blood levels and/or excretion of 1,4-DCB and its metabolites from the mother, as well as redistribution to other fat deposition sites, such as the high fat content found in breast milk.

No studies have described the interactions of 1,4-DCB with other chemicals in children, or the means by which to reduce peak absorption of 1,4-DCB after exposure.

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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to dichlorobenzenes 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 dichlorobenzenes are discussed in Section 3.8.2.

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Dichlorobenzenes

Exposure to DCBs can be identified by measuring levels of the isomers in blood (Bristol et al. 1982; Hill et al. 1995; Jan 1983; Langhorst and Nestrick 1979; Pellizzari et al. 1985), urine (Ghittori et al. 1985; Hill

et al. 1995; Kumagai and Matsunaga 1995, 1997; Zenser et al. 1997), adipose tissue (Jan 1983), and breast milk (Jan 1983; Mes et al. 1986). Toxicokinetic studies (Section 3.4) indicate that DCBs are present in blood for a limited time after exposure and eliminated from the body over a period of several days, primarily in the urine as metabolites (Hissink et al. 1996a, 1996b; Kimura et al. 1979; Parke and Williams 1955). Measurement of urinary metabolites is likely to provide a better indication of recent exposure than blood or other measurements since DCBs can be excreted for several days post-exposure (Hallowell 1959). Urinary 2,5-dichlorophenol is a well-documented biomarker for monitoring worker exposure to 1,4-DCB (McKinney et al. 1970; Pagnotto and Walkley 1965). Urinary 2,3- and 3,4-dichlorophenols, as well as 3,4- and 4,5-dichlorocatechols, have been shown to be useful indicators of exposure to 1,2-DCB (Kumagai and Matsunaga 1997). Because the basic steps in the metabolism of the three DCB isomers are similar, likely biomarkers of exposure to 1,3-DCB include 2,4- and 3,5-dichlorophenols (Kimura et al. 1992). The presence of a DCB isomer and/or its conjugates in urine is not completely specific for exposure to the DCB. For example, several chlorophenols, including 2,5-dichlorophenol, have been identified as metabolites of lindane in laboratory animals. Because DCBs tend to accumulate in fat, measurements of adipose levels of the parent isomers are likely to provide useful information on long-term exposures (Jan 1983; Morita et al. 1975). There are currently no data available to assess a potential correlation between the values obtained with these measurements and the toxic effects observed in humans or laboratory animal species. Information on the analytical methods commonly used to detect and quantify 1,4-DCB in biological samples is presented in Section 6.1.

No information is available describing specific biomarkers of exposure to 1,4-DCB in children.

3.8.2 Biomarkers Used to Characterize Effects Caused by Dichlorobenzenes

There are no known specific biomarkers of effects for 1,2-, 1,3-, or 1,4-DCB because none of the health effects identified in humans or animals appear to be uniquely associated with exposure to any isomer. Biomarkers of effects for DCBs are likely to be common to the general class of halogenated aromatic hydrocarbons because DCBs and other structurally similar chemicals cause generally similar effects. For example, DCBs and other chlorinated aromatics induce a similar spectrum of hepatic effects ranging from liver enlargement and increased microsomal enzyme activities at lower levels of exposure to degenerative lesions at higher doses.

It is well documented that 1,4-DCB induces hyaline droplet formation and tubular degeneration in the kidneys of male rats at moderate-to-high levels of oral exposure. Saito et al. (1996) studied the effect of

oral treatment with 1,4-DCB on the urinary excretion of kidney-type $\alpha_{2\mu}$-globulin (aG-K) in male Sprague-Dawley rats. Groups of 3 rats received placebo or 1,4-DCB (1.5 mmol/kg/day; 220 mg/kg/day) by gavage in corn oil for 7 days. Concentrations of aG-K in the urine of 1,4-DCB-treated rats ranged from 0.04 to 0.18 mg/mL; urine concentrations increased steadily throughout the study. In contrast, aG-K concentrations were undetectable in the urine of controls at all time points. The mean concentration of aG-K in the kidneys of rats treated with 1,4-DCB was 1.15 mg/mg of soluble protein, compared to 0.35 mg/mg protein in the control group. The authors concluded that measurement of urinary aG-K would be a good indicator of 1,4-DCB exposure; however, this response is neither unique to 1,4-DCB nor applicable to human exposure cases. As discussed earlier in Section 2.5, this particular protein is produced in large amounts by male rats, accounting for 26% of their total urinary protein, but not in human males, where it was found to be present at 1% of the amount measured in male rats (Olson et al. 1990). Also, this protein is produced in only minimal quantities by females of any species or the males of other laboratory species including mice (EPA 1991i). These observations have led to suggestions that humans are probably not at risk for the type of nephropathy induced by 1,4-DCB in male rats, and that the $\alpha_{2\mu}$-globulin biomarker is inappropriate to use in humans (EPA 1991i).

No information was available describing specific biomarkers of effect in children to 1,4-DCB.

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

3.9 INTERACTIONS WITH OTHER CHEMICALS

Little information is available regarding possible interactions of 1,2-, 1,3-, or 1,4-DCB with other chemicals. Because DCBs are liver toxins, they might interact with other chemicals that are liver toxicants. These toxicants are many, and include ethanol, halogenated hydrocarbons (chloroform, carbon tetrachloride, etc.), benzene, and other haloalkanes and haloalkenes. DCB hepatotoxicity could also be exacerbated by concurrent exposure to acetaminophen, heavy metals (copper, iron, arsenic), aflatoxins, pyrrolizidine alkaloids (from some types of plants), high levels of vitamin A, and hepatitis viruses. Such interactions are likely to be additive or synergistic. One study found that pretreatment with DCB increased LD_{50} values for parathion in mice (EPA 1985a).

Regarding the effect of 1,4-DCB on hemolysis and formation of Heinz bodies, methemaglobinemia, and hemolytic anemia, it is likely that additive or synergistic interaction would occur with other oxidants, such as aniline and acrolein, which are known to inhibit G6PD. A human case study reported a possible interactive effect between DCB and naphthalene in a woman who developed aplastic anemia (EPA 1985a).

Perinatal evaluations were performed in offspring of female Wistar rats were exposed to diets containing 25 ppm 1,4-DCB (estimated dose 2 mg/kg/day) alone or combined with 125 ppm *p,p'*-dichlorodiphenyl-dichloroethylene (*p,p*'-DDE) from Gd 1 to Pnd 21 for a total of 42 days (Makita 2005). There were no maternal effects in either group as shown by clinical signs or changes in body weight and food consumption. Perinatal evaluations showed no gross external malformations or effects on litter size, sex ratio, or pup viability on Pnd 1 in either group. Assessments of the offspring until 6 weeks of age showed no postnatal effects on body weight gain, anogenital distance, times of eye and vaginal opening and preputial separation, or serum levels of reproductive hormones (LH and FSH in both sexes and testosterone in males at 6 weeks) in either group. Examination of the liver, kidneys, spleen, thymus, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, and thymus at 6 weeks showed no effects on organ weight or histology in either group, except for increased absolute thymus weight (approximately 20% higher than controls) in female pups exposed to 1,4-DCB alone. The biological significance of this effect is unclear because it did not occur in the male offspring and was not accompanied by any histological changes. There was no effect on thymus weight or histology in male or female pups exposed to the mixture of 1,4-DCB and *p,p*'-DDE.

No information was located on interactions between DCBs and other chemicals in children.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to dichlorobenzenes than will most persons exposed to the same level of dichlorobenzenes in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of dichlorobenzenes, or compromised function of organs affected by dichlorobenzenes. Populations who are at greater risk due to their unusually high exposure to dichlorobenzenes are discussed in Section 6.7, Populations with Potentially High Exposures.

No population has been identified as exhibiting an unusual susceptibility to the effects of exposure to 1,4-DCB. However, based on data from studies in humans and animals, individuals with compromised liver function, infants and children with immature liver function (Hallowell 1959), and elderly people (Cotter 1953; Nalbandian and Pearce 1965) may be more at risk than the general population. Individuals having a genetic susceptibility to methemoglobin formation (such as those individuals with a deficiency of G6PD in their red blood cells) may also be at increased risk from inhalation or oral exposure to 1,4-DCB.

No information was available describing specific susceptibilities of children to 1,4-DCB. There is no direct evidence that children differ in their susceptibility to the health effects of 1,4-DCB from adults. It should be noted that postnatal neurodevelopmental toxicity is a sensitive end point in 1,4-DCB-exposed rats (Bornatowicz et al. 1994), suggesting a basis for potential concern in exposed children. This issue is discussed in detail in Section 3.7 Children's Susceptibility.

The extent to which men and women may differ in susceptibility to DCBs is not known. Available animal data do not provide a clear pattern for gender differences in the toxicity of DCBs, although some subchronic and chronic studies found that males were more sensitive than females for some end points. For example, a multigeneration inhalation study of 1,4-DCB in rats observed increases in adult liver weight that were more pronounced in males than females (Tyl and Neeper-Bradley 1989). In a subchronic oral study of 1,3-DCB in rats, histopathological changes in the thyroid were generally more severe in males than in females (McCauley et al. 1995). This study also found histopathology in the pituitary of male rats, but not female rats. The pituitary lesion was reported to be similar to those induced in gonadectomized rats and was considered to be an indicator of gonadal deficiency (McCauley et al. 1995). Though these animal studies provide an indication that males may be more sensitive to DCBs exposure, the evidence is insufficient for extrapolating to humans.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to dichlorobenzenes. 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 dichlorobenzenes. When specific exposures have occurred, poison control centers and medical toxicologists should be

consulted for medical advice. The following texts provide specific information about treatment following exposures to dichlorobenzenes:

Aaron CK, Howland MA, eds. 1994. Goldfrank's toxicologic emergencies. Norwalk, CT: Appleton and Lange.

Dreisback RH, ed. 1987. Handbook of poisoning. Norwalk, CT: Appleton and Lange.

Ellenhorn MJ, Barceloux, DG, eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier Publishing.

Grossel TA, Bricker JD. 1994. Principles of clinical toxicology. 3rd edition, New York, NY: Raven Press.

Haddad LM, Winchester JF, eds. 1990. Clinical management of poisoning and drug overdose. 2nd edition, Philadelphia, PA: WB Saunders.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to 1,4-DCB can occur by inhalation, ingestion, or dermal contact. General recommendations for reducing absorption of 1,4-DCB following acute-duration inhalation exposure have included moving the patient to fresh air and administration of 100% humidified supplemental oxygen with assisted ventilation (HSDB 1996). General recommendations for reducing absorption following acute ingestion exposure have included inducing vomiting (unless the patient is or could rapidly become obtunded, comatose, or convulsing, and considering the risk of aspiration of vomitus), gastric lavage, or administration of a charcoal slurry (HSDB 1996). Intake of fatty foods, which would promote absorption, should be avoided. In the case of eye exposure, irrigation with copious amounts of water has been recommended (HSDB 1996). For dermal exposure, and to minimize dermal absorption, the removal of contaminated clothing and a thorough washing of any exposed areas with soap and water has been recommended (HSDB 1996).

3.11.2 Reducing Body Burden

1,4-DCB distributes to fatty tissues and is probably retained there at low concentrations (EPA 1986d; Hawkins et al. 1980; Morita and Ohi 1975; Morita et al. 1975). However, most of an absorbed dose is excreted within 5 days of exposure (Hawkins et al. 1980), and there is no evidence suggesting that the low levels of 1,4-DCB that are likely to remain in fatty tissues would cause adverse effects. For these reasons,

methods for enhancing elimination of 1,4-DCB shortly after high-dose exposure could reduce toxic effects; however, no such methods have been identified. Methods that could enhance the elimination of 1,4-DCB after high- or low-dose exposure in humans or laboratory animals have not been reported.

While it might be possible to develop methods to alter metabolism of 1,4-DCB to promote formation of metabolites that are more easily excreted, this could be difficult because the current lack of knowledge of the specific metabolic pathways of 1,4-DCB precludes speculation concerning which pathways it might be most beneficial to stimulate or inhibit. One pathway for which stimulation may be contraindicated is sulfate conjugate formation (Kimura et al. 1979). Methylation of 1,4-DCB sulfate conjugates can occur, and these methylated conjugates are excreted less rapidly than nonmethylated conjugates (Kimura et al. 1979). Since little is known concerning the toxicity of these conjugates, it is presently not possible to determine the consequences of promoting formation of these metabolites.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action for liver effects of 1,4-DCB has not been clearly delineated; however, based on *in vitro* experiments, induction of P-450 metabolism by pretreatment with phenobarbital may enhance hepatotoxicity (Fisher et al. 1991a). This suggests that one mechanism of hepatotoxicity may be the production of reactive intermediates through phase I P-450-mediated oxidation, although it should be noted that the P-450 inhibitors metyrapone and SKF 525-A did not block hepatotoxicity of 1,4-DCB in human liver tissue *in vitro* (Fisher et al. 1991a). Lattanzi et al. (1989) provide evidence indicating that the microsomal mixed-function oxidase system and microsomal glutathione transferases and, to a lesser degree, cytosolic glutathione transferases, can be involved in the bioactivation of 1,4-DCB. More information concerning the mechanism of action for hepatic effects is needed before methods for blocking that mechanism and reducing toxic effects can be developed.

The mechanisms of action for nephrotoxic (with the exception of $\alpha_{2\mu}$-globulin-mediated nephropathy specific to male rats) or hematotoxic effects have not been clearly delineated, and with the available information, it is difficult to speculate how 1,4-DCB might cause such effects. More information concerning the mechanisms of action for blood and kidney effects are needed before methods for blocking those mechanism and reducing toxic effects can be developed.

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 dichlorobenzenes 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 dichlorobenzenes.

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 Dichlorobenzenes

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to dichlorobenzenes are summarized in Figures 3-7, 3-8, and 3-9. The purpose of this figure is to illustrate the existing information concerning the health effects of dichlorobenzenes. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Some limited information (i.e., anecdotal, single acute-duration exposure, and workplace exposure) is available on the health effects of human exposure to 1,2- and 1,4-DCB via inhalation and 1,4-DCB by the oral route. For persons exposed via inhalation, there is information on death, systemic effects, neurologic effects. There is also information on systemic effects in humans resulting from acute-, intermediate-, and chronic-duration oral exposure. It is important to note that most of this oral information was obtained from case studies in which levels and durations of exposure to 1,4-DCB were unknown or uncertain.

Figure 3-7. Existing Information on Health Effects of 1,2-Dichlorobenzene

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

Human

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

Animal

● Existing Studies

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

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

Human

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

Animal

● Existing Studies

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

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

Human

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

Animal

● Existing Studies

Data available on health effects of DCBs in animals are more extensive than in humans. Most of the information is for 1,2- and 1,4-DCB, whereas all data on 1,3-DCB are from one oral study. The most extensively studied isomer is 1,4-DCB. Information is available on the developmental, reproductive, genotoxic, and carcinogenic effects of inhalation exposure to 1,4-DCB, as well as on the systemic effects resulting from intermediate-duration exposure. In studies using oral exposure, information is available on death; systemic effects resulting from acute-, intermediate-, and chronic-duration exposure; and developmental, genotoxic, and carcinogenic effects. Only data on the lack of a lethal effect are available in studies using dermal exposure.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. A limited amount of information is available on health effects in people who were occupationally exposed to 1,2-DCB (Hollingsworth et al. 1958). This information includes exposure levels associated with eye and respiratory tract irritation and results of periodic medical examinations, but the data are insufficient for identifying sensitive systemic end points in humans or for inhalation MRL derivation purposes. The limited information on irritation effects of 1,2-DCB in humans is consistent with histological findings of nasal olfactory epithelial lesions in mice that were intermittently exposed to 1,2-DCB vapor for up to 14 days (Zissu 1995). The severity of the nasal lesions ranged from moderate to severe in severity and occurred at concentrations lower than those that caused acute systemic effects (liver and kidney lesions) in rats (DuPont 1982; Hollingsworth et al. 1958) or developmental effects in rats and rabbits (Hayes et al. 1985). A NOAEL was not identified for the serious nasal effects, precluding derivation of an acute inhalation MRL. Additional studies could characterize the threshold region for nasal effects, confirm that the nasal cavity is more sensitive than systemic end points, and provide a sufficient basis for inhalation MRL derivation.

There is no information on the toxicity of 1,2-DCB in orally-exposed humans. Information on effects of acute oral exposure to 1,2-DCB in animals essentially consists of findings in three systemic toxicity studies in rats and mice (NTP 1985; Rimington and Ziegler 1963; Robinson et al. 1991) and one developmental toxicity study in rats (Ruddick et al. 1983). These studies collectively identify the liver as the most sensitive target, but two are limited by small numbers of animals and lack of a NOAEL due a single dose level (Rimington and Ziegler 1963) or lack of histopathology evaluations at doses lower than the LOAEL (NTP 1985). The third systemic toxicity study (Robinson et al. 1991) is well designed, identified a critical NOAEL and LOAEL for hepatoxicity, and was used to derive an acute oral MRL.

Additional studies are needed to establish whether liver toxicity is the most sensitive end point for acute exposure and the most appropriate basis for the MRL. The oral database for 1,2-DCB particularly lacks adequate assessments of neurotoxicity, immunotoxicity, and end points shown to be sensitive to other DCB isomers (e.g., thyroid and pituitary).

No inhalation toxicity data are available for 1,3-DCB in humans or animals, indicating that a well-designed inhalation toxicity study could provide a basis for an acute inhalation MRL. The acute oral database for 1,3-DCB essentially consists of one well-designed 10-day systemic toxicity study (McCauley et al. 1995) that was sufficient for estimation of an MRL. Additional studies could determine whether the critical effect in this study, increased liver weight, is the most appropriate and sensitive end point for MRL derivation.

A limited amount of information is available on the toxicity of inhaled 1,4-DCB in humans. Case reports of people who inhaled 1,4-DCB provide indications that the liver and nervous system are systemic targets of inhalation toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-DCB was the only factor associated with the effects (Cotter 1953; Miyai et al. 1988; Reygagne et al. 1992). An occupational health survey identified odor detection and eye/nose irritation thresholds for 1,4-DCB (Hollingsworth et al. 1956). Information on effects of acute-duration inhalation exposure to 1,4-DCB in animals is available from short-term systemic toxicity studies in rats and guinea pigs (Hollingsworth et al. 1956), a male reproduction study rats (Anderson and Hodge 1976), and developmental toxicity studies in rats and rabbits (Hayes et al. 1985; Hodge et al. 1977). These animal studies identified the lung as the target of concern, and are consistent with chronic inhalation data (Aiso et al. 2005b; Japan Bioassay Research Center 1995) as well as the human occupational experience (Hollingsworth et al. 1956), but are insufficient for deriving an acute inhalation MRL. Studies in animals investigating potentially sensitive systemic end points (e.g., respiratory, endocrine, neurological, immunological) are needed to identify an appropriate end point and effect level for MRL derivation.

Information on effects of non-lethal acute-duration oral exposures to 1,4-DCB is essentially limited to hepatic and renal changes of unclear toxicological significance observed in animal studies designed to elucidate mechanisms of liver and kidney toxicity in rats and mice. Appropriately designed acute oral studies are needed to provide a suitable basis for MRL derivation.

The only available study using the dermal route is a lethality study that attempted to determine a dermal LD_{50} level for 1,4-DCB in rats (Gaines and Linder 1986). There are no available toxicokinetic data that

have examined absorption of 1,4-DCB via the dermal route. If dermal absorption and systemic distribution of 1,4-DCB could be demonstrated, acute-duration studies using this route would be useful since humans are commonly exposed to it by handling various consumer products in the home and being exposed to the vapor form.

Intermediate-Duration Exposure. Information on the toxicity of intermediate-duration inhalation exposure to 1,2-DCB is limited to the findings of a multispecies subchronic study (Hollingsworth et al. 1958) and a 2-generation reproduction study in rats (Bio/dynamics 1989). These studies identified NOAELs and LOAELs for liver and body weight effects, but possible effects in the nasal cavity, a known sensitive target of 1,2-DCB based on acute data, were not evaluated. Derivation of an intermediate-duration inhalation MRL for 1,2-DCB is precluded because the acute-duration serious LOAEL for nasal effects (Zissu 1995) is lower than the available intermediate-duration LOAELs for systemic and developmental effects. Additional studies could verify the nasal cavity is more sensitive than systemic end points and provide exposure-response data useful for inhalation MRL derivation.

No information was located regarding the toxicity of inhaled 1,3-DCB in humans or animals, indicating that appropriate studies are needed to provide a basis for derivation of an intermediate-duration inhalation MRL for this isomer. The database for intermediate-duration oral exposure to 1,3-DCB consists of one well-designed 90-day systemic toxicity study (McCauley et al. 1995) that was sufficient for estimation of an intermediate oral MRL. The thyroid, pituitary, and liver were identified as sensitive targets and incidences of pituitary lesions were used to derive an intermediate oral MRL.

Case studies are available on humans exposed to 1,4-DCB via inhalation and the oral route for intermediate-duration exposure. These include the report of a 69-year-old man who developed skin discolorations and swelling of his hands and feet after about 3 weeks of exposure to 1,4-DCB in his home (Nalbandian and Pearce 1965), the cases of a 60-year-old man and his wife who both died of liver atrophy after their home had been saturated with moth ball vapor for 3–4 months (Cotter 1953), and the case of a 21-year-old woman who developed hypochromic, microcytic anemia as a result of ingesting 1,4-DCB toilet air freshener blocks throughout pregnancy (Campbell and Davidson 1970). All of these case studies lack critical dosing amounts and durations. It would be helpful if future reports of accidental or intentional exposure included dose information (measured or estimated) that could be used to help characterize dose-response relationships in humans.

Information on effects of intermediate-duration inhalation exposure to 1,4-DCB in animals is available from a multispecies subchronic toxicity study (Hollingsworth et al. 1956), a 13-week toxicity study in rats and mice (Aiso et al. 2005a), and a 2-generation reproductive/developmental toxicity study in rats (Tyl and Neeper-Bradley 1989). The 13-week and 2-generation studies identified a NOAEL and LOAEL for increased relative liver weight, and increased liver weight was used to derive an MRL. A chronic inhalation study (Aiso et al. 2005b; Japan Bioassay Research Center 1995) found that nasal lesions in rats and testicular effects in mice were more sensitive than liver effects. No nasal or testicular lesions were reported in the 13-week rat and mouse study, and these tissues were not examined in the multispecies subchronic study. Additional studies could verify that liver weight is the most appropriate basis for the intermediate inhalation.

Information on the systemic toxicity of intermediate-duration oral exposure to 1,4-DCB is available from a number of studies conducted in rodents, mainly rats and mice, as well as one study in dogs (Bomhard et al. 1988; Hollingsworth et al. 1956; NTP 1985; Lake et al. 1997; Naylor and Stout 1996; Umemura et al. 1998). Liver and kidney effects were the most consistently observed, best characterized, and most sensitive findings in these studies. Liver effects were used as the basis for intermediate-duration oral MRLs for 1,2-DCB (NTP 1985) and 1,4-DCB (Naylor and Stout 1996).

Studies using the dermal route for intermediate-duration exposure would be useful if absorption and systemic distribution of 1,4-DCB by this route could first be demonstrated in toxicokinetic studies.

Chronic-Duration Exposure and Cancer. No studies were located regarding the chronic inhalation toxicity of 1,2-DCB in humans or animals, indicating that data are needed to provide a basis for estimation of an inhalation MRL. Regarding chronic oral toxicity of 1,2-DCB, the only available study is a two-dose-level NTP (1985) bioassay that was conducted in rats and mice. The only exposure-related effect in either species was a significantly increased incidence of renal tubular regeneration in male mice. A NOAEL and LOAEL were identified for this lesion and incidences of renal tubular regeneration were used to derive a chronic oral MRL for 1,2-DCB. No information is available on the carcinogenicity of 1,2-DCB in humans. Data on cancer in animals are limited to the NTP (1985) chronic bioassay, in which no exposure-related tumors were found in male and female rats and mice exposed to two dose levels of 1,2-DCB for 103 weeks. This is a well-designed chronic study with respect to exposure duration and scope of histological examinations, but it is uncertain whether an MTD was achieved in either species. Additional studies that include multiple dose levels and clear MTDs, as well as toxicity end points that could be more sensitive than kidney lesions (e.g., endocrine and immunological), could be used determine

if the MRL is based on the most appropriate effect level and also provide an better assessment of carcinogenic potential.

No studies were located regarding the chronic inhalation or oral toxicity of 1,3-DCB in humans or animals, indicating that data are needed to provide the bases for chronic MRL and carcinogenicity assessments.

Several case studies of chronic human exposure to 1,4-DCB have been reported. Reported effects resulting mainly from chronic inhalation included pulmonary granulomatosis in a 53-year-old woman who had been inhaling 1,4-DCB crystals in her home for 12–15 years (Weller and Crellin 1953); atrophy and cirrhosis of the liver in a 34-year-old woman who was exposed to 1,4-DCB-containing products in a small enclosed booth in a department store for 1 or more years (Cotter 1953); jaundice and liver atrophy in a 52-year-old man after 2 years of exposure to 1,4-DCB in the fur storage plant where he worked (Cotter 1953); and ataxia, speech difficulties, limb weakness, and altered brainwave activity in a 25-year-old woman who had been exposed to high concentrations of 1,4-DCB in her bedroom, bedding, and clothes for about 6 years (Miyai et al. 1988). A limited occupational health survey reported that nasal and ocular irritation, but no major systemic health effects, were the only 1,4-DCB-related complaints (Hollingsworth et al. 1956). Further occupational health data on individuals exposed chronically to 1,4-DCB would be useful for both cancer and noncancer health effect end points already mentioned. The only data located relating to chronic oral human exposure to 1,4-DCB come from a case report of a 19-year-old black woman who developed an increase in skin pigmentation as a result of eating 1,4-DCB moth pellets daily for about 2.5 years (Frank and Cohen 1961). All of these case studies lacked dosing amounts and durations, which makes it difficult to characterize dose-response relationships for effects in humans exposed to 1,4-DCB. No studies of chronic dermal exposure to 1,4-DCB were located, although it seems likely that chronic inhalation and oral exposure scenarios, both in the home and in the workplace, have also involved dermal contact with 1,4-DCB.

A limited amount of additional information is available on the chronic toxicity of inhaled 1,4-DCB in humans. Periodic health examinations of workers who were exposed to 1,4-DCB for an average of 4.75 years (range, 8 months to 25 years) showed no changes in standard blood and urine indices (Hollingsworth et al. 1956). The data from this occupational study are inadequate for chronic MRL derivation due to poor characterization of exposure levels, insufficient investigation of systemic health end points, and poor reporting as well as other study deficiencies. However, eye and nose irritation findings in this study are consistent with nasal effects observed in chronically exposed animals.

Information on the chronic inhalation toxicity of 1,4-DCB in animals is available from two studies in rats and mice (Aiso et al. 2005b; Japan Bioassay Research Center 1995; Riley et al. 1980a, 1980b). One of these studies (Aiso et al. 2005b; Japan Bioassay Research Center 1995) identified nasal lesions in rats and provided a sufficient basis for MRL estimation.

Information on the chronic oral effects of 1,4-DCB is available from one study each in rats, mice, and rabbits (Hollingsworth et al. 1956; NTP 1987). Lesions were observed in the kidneys and liver, and the lowest tested dose was a LOAEL for renal effects in rats (NTP 1987). Naylor and Stout (1996) identified liver effects (increased liver weight, changes in liver enzymes, and histopathology) in dogs administered 1,4-DCB for 1 year; these liver effects provided a sufficient basis for chronic oral MRL estimation. Information on carcinogenicity of 1,4-DCB is available from the chronic oral and inhalation studies in rats and mice. The oral study (NTP 1987) found evidence of carcinogenicity based on increased tumor incidences in male rat kidneys and in the livers of male and female mice. The kidney tumors are not relevant to humans because the mechanism ($\alpha_{2\mu}$-globulin nephropathy) is specific to male rats. One of the inhalation studies (Aiso et al. 2005b; Japan Bioassay Research Center 1995) similarly showed tumor induction in the livers of male and female mice, although there was no tumor formation in either sex of rats. The other inhalation study (Riley et al. 1980a, 1980b) found no neoplastic changes in rats or mice, but the adequacy of the study for carcinogenicity evaluation is limited by failure to reach the maximum tolerated dose, less-than-lifetime exposure durations, and short observation periods in both species. There is sufficient evidence of 1,4-DCB carcinogenicity in animals based on the induction of liver tumors in mice exposed by both the oral and inhalation routes. Unlike the kidney tumors in male rats, the mechanistic basis of the liver tumors in mice is not adequately defined, indicating that additional studies could help to better assess their relevance to humans.

Data on the effects of chronic dermal exposure to 1,4-DCB might be useful if dermal absorption and systemic distribution of 1,4-DCB can be demonstrated from toxicokinetic studies, since chronic dermal exposure to 1,4-DCB occurs as a result of bathing and showering in drinking water that contains low levels of this chemical in many U.S. communities.

Genotoxicity. Genotoxic effects of 1,2- and 1,3-DCB have been investigated in various animal test systems with generally mixed results. The genotoxicity of 1,4-DCB has been extensively studied in a wide variety of *in vitro* and *in vivo* animal assays with a preponderance of negative results. Additional studies could help to clarify the mechanism of carcinogenesis for 1,4-DCB-induced liver tumors in mice.

There are considerable data supporting a sustained proliferative response following 1,4-DCB exposure as the mode of action for liver tumor formation; however, the existing evidence is incomplete.

Reproductive Toxicity. The reproductive toxicity of 1,2-DCB has been evaluated in a 2-generation inhalation study in rats (Bio/dynamics 1989), but not by the oral route. The inhalation study found no effects on reproduction in either generation at exposure levels higher than those causing liver effects in the parental animals, indicating that it can be used to partially address the data gap for oral exposure.

No information was located on possible reproductive effects of 1,3-DCB, indicating that reproductive toxicity is a data need for both inhalation and oral exposure to this isomer.

The reproductive toxicity of 1,4-DCB has been evaluated in inhalation and oral 2-generation studies in rats with no exposure-related effects on reproductive function (Bornatowicz et al. 1994; Tyl and Neeper-Bradley 1989). An inhalation study of male mice exposed to 1,4-DCB for 5 days did not find an adverse impact on their ability to impregnate females (Anderson and Hodge 1976). Incidences of morphologically abnormal sperm were increased in rats that were intraperitoneally injected with 1,4-DCB (Murthy et al. 1987). Histopathology evaluations of 1,4-DCB-exposed animals have not demonstrated changes in reproductive tissues in the preponderance of studies. Based on the available data, there is no compelling need for additional reproductive toxicity studies of 1,4-DCB.

Developmental Toxicity. The developmental toxicity of inhaled 1,2-DCB was evaluated in an adequate study of gestationally-exposed rats and rabbits (Hayes et al. 1985). Skeletal variations, but no teratogenic effects, occurred in rats at a concentration that also caused maternal toxicity. A poorly reported oral study in which rats were gestationally exposed to 1,2-DCB (Ruddick et al. 1983) found no effects on fetuses and indicates that developmental toxicity, if induced, would only occur at levels that were maternally toxic. No information is available on possible neurodevelopmental effects of 1,2-DCB, indicating that this is a data need.

No information was located on the developmental toxicity of 1,3-DCB, indicating that this is a data need for both inhalation and oral exposure to this isomer.

The developmental toxicity of inhaled 1,4-DCB was evaluated in adequate studies of gestationally-exposed rats and rabbits (Hayes et al. 1985; Hodge et al. 1977). No maternal or prenatal developmental toxicity occurred in the rats, although there was evidence of fetotoxicity (a minor variation of the

circulatory system) in the rabbits at a concentration that was maternally toxic and higher than LOAELs for systemic toxicity in other studies. Information on developmental toxicity of ingested 1,4-DCB is available from an 2-generation oral study in rats (Bornatowicz et al. 1994). Fetuses were not examined for prenatal changes, but various effects occurred in the offspring perinatally and during the later pre-weaning period, including decreased neonatal survival and impaired neurobehavioral development in F_1 and F_2 pups. This finding suggests that postnatal neurobehavioral development is a sensitive end point for 1,4-DCB that could be better characterized by additional studies.

Immunotoxicity. No information is available on immunological function in humans or animals exposed to 1,2-DCB or 1,3-DCB by the inhalation or oral routes. Lymphoid depletion in the thymus was observed histologically in rats that were exposed to a high oral dose of 1,2-DCB for 13 weeks (NTP 1985), suggesting that the immune system is a possible target of concern and providing an additional indication of the need for adequate assessments of immunotoxicity.

No studies were located that directly assess the potential immunotoxic effects of 1,4-DCB in humans exposed by inhalation, oral, or dermal routes. However, case reports of skin reactions in a 69-year-old man who was exposed via inhalation (Nalbandian and Pearce 1965) and a 19-year-old woman who ingested moth pellets (Frank and Cohen 1961) suggest that the immune system may be a target for 1,4-DCB. Oral exposure to high doses of 1,4-DCB for 13 weeks caused lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia in the spleen and bone marrow of mice, and lymphoid depletion of the thymus and spleen in rats (NTP 1987). Effects of oral 1,4-DCB exposure on function of the immune system have not been studied, although there were no functional decrements in a 12-week inhalation immunotoxicity study in guinea pigs that assessed a limited number of indices (Suzuki et al. 1991). Comprehensive immunological testing would help to adequately assess the immunotoxic potential of 1,4-DCB.

Neurotoxicity. Comprehensive neurobehavioral assessments have not been performed for any of the DCB isomers. Clinical signs neurotoxicity (e.g., ataxia and clonic contractions) were observed in rats that were orally exposed to a high dose of 1,2-DCB for 15 days (Rimington and Ziegler 1963), but similar effects were not found in rats or mice in other studies of this isomer. No signs of neurotoxicity occurred in rats were orally exposed to 1,3-DCB for up to 90 days (McCauley et al. 1995).

Neurological effects including dizziness, weakness, headaches, nausea, vomiting, numbness, clumsiness, speech difficulties, and altered patterns of certain brainwaves have been reported to have occurred in case

studies of persons exposed to 1,4-DCB via inhalation (Cotter 1953; Miyai et al. 1988), as well as with other halogenated hydrocarbons. There are no data on neurological effects in humans exposed to 1,4-DCB through the oral or dermal routes. Neurotoxic effects of 1,4-DCB occurred in rats, rabbits, and guinea pigs following inhalation exposure to high concentrations; effects included tremors, weakness, and periods of unconsciousness. Similar neurological responses were observed following oral exposure to high doses of 1,4-DCB (NTP 1987; Rimington and Ziegler 1963). No studies were located that reported neurological effects after a dermal route of exposure. Additional information, particularly on subtle behavioral changes at low levels of inhalation and oral exposure, is needed to adequately assess the neurotoxic potential of 1,4-DCB and for quantifying dose-response relationships.

Epidemiological and Human Dosimetry Studies. A limited amount of information is available on the inhalation toxicity of 1,2- and 1,4-DCB in humans from observations in exposed workers, mainly from assessments of symptoms and standard blood and urine indices as determined by periodic occupational health examinations (Hollingsworth et al. 1956, 1958). No information is available on the toxicity of ingested 1,2- or 1,3-DCB in humans. Information on toxic effects of 1,4-DCB in orally exposed humans is limited to two case reports describing hematological changes, particularly anemia, following known or presumed repeated ingestion of unknown doses of the compound in commercial products (Campbell and Davidson 1970; Hallowell 1959). The limited available information suggests that inhalation or oral exposure to DCBs can cause effects in humans similar to those found in animals, particularly in the respiratory tract, liver, and hematological systems. There are no case studies or epidemiological data that suggest that levels of DCBs found in the environment are associated with significant human exposure. The available data suggest that levels of DCBs in outside air are relatively insignificant, although the compounds are widespread (IARC 1982; Scuderi 1986; Wallace et al. 1986b). Levels in groundwater and surface water are also relatively low (Coniglio et al. 1980; Dressman et al. 1977; IJC 1989; Oliver and Nicol 1982a; Page 1981; Staples et al. 1985). These observations indicate that the most likely population to exhibit effects of DCB exposures would be occupationally exposed groups. Human epidemiological studies that provide a more definitive dose-response relationship between exposure, clinical manifestations, and target organ toxicity (i.e., hepatic, hematological, and neurological systems) would be useful.

Biomarkers of Exposure and Effect.

Exposure. Exposure to DCBs can be identified by measuring levels of the isomers in blood (Bristol et al. 1982; Hill et al. 1995; Jan 1983; Langhorst and Nestrick 1979; Pellizzari et al. 1985), urine (Ghittori et al.

1985; Hill et al. 1995; Kumagai and Matsunaga 1995, 1997; Zenser et al. 1997), adipose tissue (Jan 1983), and breast milk (Jan 1983; Mes et al. 1986), as well as metabolites in the urine. Urinary 2,5-dichlorophenol is a well-documented biomarker for monitoring worker exposure to 1,4-DCB (McKinney et al. 1970; Pagnotto and Walkley 1965), and urinary 2,3- and 3,4-dichlorophenols, as well as 3,4- and 4,5-dichlorocatechols, have been shown to be useful indicators of exposure to 1,2-DCB (Kumagai and Matsunaga 1997). Additional data with which to correlate these measurements to exposure levels, particularly by the inhalation route, and potential health effects, would be useful.

Effect. There are no health effects that are uniquely associated with exposure to DCBs. Therefore, studies to identify a specific biomarker of effect for DCBs would be useful.

Absorption, Distribution, Metabolism, and Excretion. There are no data on the toxicokinetics of any DCB isomer in humans. Experiments with laboratory animals indicate that DCBs are absorbed via oral or inhalation exposure and distributed mainly to adipose tissue, with some distribution to the liver and kidney, and minor amounts to other organs (Hawkins et al. 1980; Kimura et al. 1979). Absorbed DCBs are principally metabolized to dichlorophenol metabolites (e.g., 2,5-dichlorophenol from 1,4-DCB) by oxidation and is rapidly eliminated, primarily in urine (Azouz et al. 1955; Hawkins et al. 1980). The available data indicate that the route of exposure is likely to have little effect on the subsequent metabolism and excretion of DCBs. Scant data are available on absorption and systemic distribution resulting from exposure via the dermal route. Dermal absorption data would be particularly useful considering that the inhalation MRLs are based on whole-body exposure. 1,4-DCB produces a burning sensation when applied to the skin for a prolonged period of time, indicating at least minimal penetration to nerve endings within the skin (Hollingsworth et al. 1956). The little information that is available suggests that dermal exposure is associated with low systemic toxicity in both humans and laboratory animals. It would be useful to confirm this because it could provide a basis for assessing the likelihood of toxic effects resulting from dermal exposure and the need to conduct various toxicity studies via the dermal route. Additional toxicokinetic data would be useful for quantitating route-specific absorption rates.

Comparative Toxicokinetics. There are no available studies that compare the toxicokinetics of any of the DCB isomers across species. This has been an important area of concern in interpreting the results of animal studies with 1,4-DCB with respect to their relevance to humans, most notably in the observations of renal toxicity and carcinogenicity in male rats. Although this specific issue has been largely resolved, it would be useful to have further data comparing the toxicokinetics of 1,4-DCB across

species in order to understand better which animal model is likely to compare most directly with humans with regard to other toxic effects in response to 1,4-DCB exposure. From the available data in humans and laboratory animals, the primary metabolite produced after exposure to 1,4-DCB is 2,5-dichlorophenol. This metabolite appears mainly in the urine after undergoing phase II metabolism, principally to the sulfate and glucuronide conjugates, with some exiting via the bile (Azouz et al. 1955; Fisher et al. 1995; Hissink et al. 1997a; Hallowell 1959; Kimura et al. 1979; Klos and Dekant 1994).

Methods for Reducing Toxic Effects. Based on the chemical and physical properties of DCBs, absorption is most likely to occur by passive diffusion. However, this has not been investigated. Studies that investigate the mechanism by which DCBs are absorbed could be useful in developing methods for reducing its absorption. Standard methods exist for reducing the absorption of DCBs across the skin, lungs, and gastrointestinal tract (HSDB 1996) and are described in more detail in Chapter 7 of this profile; however, none of these are specific for exposures to 1,2-, 1,3-, or 1,4-DCB. DCBs can be retained in fatty tissues at low levels (EPA 1986f; Hawkins et al. 1980; Morita and Ohi 1975; Morita et al. 1975). Additional studies that characterize the metabolic pathways that enhance excretion may be useful in developing a method for reducing body burden. However, since most of an absorbed dose is likely to be eliminated within several days (Hawkins et al. 1980), it seems unlikely that methods for reducing body burden would be of much benefit. There is limited evidence that DCBs are metabolically activated to hepatotoxic intermediates (Fisher et al. 1991a; Lattanzi et al. 1989). Additional studies that further characterize the metabolic activation of DCBs could be useful for understanding how metabolites interact and to develop methods for interfering with the mechanism of action.

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.

Essentially all of the studies on effects of exposure of humans to DCBs have focused on adults. It is unknown whether children differ from adults in their susceptibility to health effects from DCBs. Only two case reports of 1,4-DCB specifically referenced potential exposure to a child (Campbell and Davidson 1970; Hallowell 1959). Data relating to health effects in general for children are lacking. There are no data describing the developmental effects in humans. Such data, although potentially useful, would be difficult to obtain. See the Developmental Toxicity subsection above for related data needs.

Although there is no reason to suspect that the pharmacokinetics of DCBs differs in children and adults, scant data are available to support or disprove this statement. Studies of absorption, distribution, metabolism, and excretion in children would aid in determining if children are at an increased risk, particularly if conducted in an area where a high-dose acute or low-dose chronic exposure to an environmental source were to occur. With regard to exposure during development, additional research on maternal and fetal/neonatal toxicokinetics, placental biotransformation, the mechanism of action in children, and the risk associated with the transfer of DCBs to an infant via breast milk would be useful in obtaining a more complete picture of prenatal and neonatal development. Direct evidence on whether DCBs crosses the placenta and on the kinetics associated with that transfer is also needed. Data needs exist for determining if specific biomarkers of exposure or effect exist in children (and how those differ from adults) and how DCBs interact with other chemicals (i.e., other organochlorine pesticides, drugs, etc.) Data needs also exist for methods to reduce peak absorption after exposure, to reduce body burden, and to interfere with the mechanism of action for toxic effects targeted for adults as well as for children.

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

3.12.3 Ongoing Studies

No known ongoing studies related to the toxicity or toxicokinetics of DCBs were identified.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Dichlorobenzenes (DCBs) are chlorinated aromatic compounds. 1,2-DCB is used primarily as a precursor for 3,4-dichloroaniline herbicides (CMR 1996). 1,3-DCB is used in the production of various herbicides, insecticides, pharmaceuticals, and dyes (Krishnamurti 2001). 1,4-DCB is used as a deodorant for restrooms (Howard 1989), for moth control (O'Neil 2001), and as an insecticide (Farm Chemicals Handbook 1983). Information regarding the chemical identity of 1,2-, 1,3-, and 1,4-DCB is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The dichlorobenzene isomers, 1,2-DCB and 1,3-DCB, are colorless volatile liquids at room temperature (EPA 1985a). 1,2-DCB has a pleasant odor, while the odor of 1,3-DCB is unspecified (EPA 1985a; NIOSH 2005). 1, 4-DCB is a combustible crystalline solid that tends to sublime at ordinary room temperatures. It possesses a distinctive odor reportable to be noticeable at airborne concentrations between 30 and 60 ppm (by weight [ppm-w] or by volume [ppm-v] not specified; presumably "ppm" would refer to ppm by weight). Information regarding the physical and chemical properties of 1,2-, 1,3-, and 1,4-DCB is located in Table 4-2.

Table 4-1. Chemical Identity of 1,2-, 1,3-, and 1,4-Dichlorobenzene

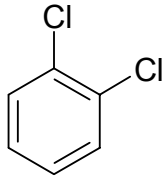
Characteristic	Value	Reference
Chemical name	1,2-Dichlorobenzene	Lide 2000
Synonyms	o-Dichlorobenzene; o-dichlorobenzol; orthodichlorobenzene	RTECS 2005
Trade names	Chloroben; Cloroben; Dilatin DB; Dowtherm E; Dizene; Special termite fluid; Termitkil	HSDB 2005; RTECS 2005
Chemical formula	$C_6H_4Cl_2$	RTECS 2005
Chemical structure		
Identification numbers:		
CAS Registry	95-50-1	Lide 2000
NIOSH RTECS	CZ4500000	RTECS 2005
EPA Hazardous Waste	U070; F002	HSDB 2005
OHM/TADS	No data	
DOT/UN/NA/IMCO Shipping	UN 1591; IMO 6.1	HSDB 2005
HSDB	521	HSDB 2005
NCI	NCI-C54944	RTECS 2005

Table 4-1. Chemical Identity of 1,2-, 1,3-, and 1,4-Dichlorobenzene

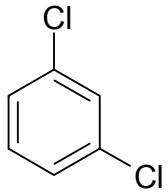
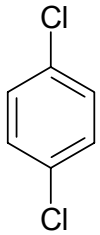
Characteristic	Value	Reference
Chemical name	1,3-Dichlorobenzene	Lide 2000; HSDB 2005
Synonyms	m-Dichlorobenzene; m-DCB; m-dichlorobenzol; m-phenylene dichloride	RTECS 2005
Trade names	No data	
Chemical formula	$C_6H_4Cl_2$	RTECS 2005
Chemical structure		
Identification numbers:		
CAS Registry	541-73-1	Lide 2000
NIOSH RTECS	CZ4499000	RTECS 2005
EPA Hazardous Waste	U071	HSDB 2005
OHM/TADS	No data	
DOT/UN/NA/IMCO Shipping	No data	
HSDB	522	HSDB 2005
NCI	No data	

Table 4-1. Chemical Identity of 1,2-, 1,3-, and 1,4-Dichlorobenzene

Characteristic	Value	Reference
Chemical name	1,4-Dichlorobenzene	Lide 2000
Synonyms	para-Dichlorobenzene; p-dichloro-benzene; p-chlorophenyl chloride; PDB; PDCB; p-dichlorobenzol	RTECS 2005
Trade names	Paracide; Paradow; Paradi; Santochlor; Paramoth; Paranuggets; Parazene; Persia-perazol; Para crystals; Global; Evola; Di-chloricide	RTECS 2005
Chemical formula	$C_6H_4Cl_2$	RTECS 2005
Chemical structure		
Identification numbers:		
CAS Registry	106-46-7	Lide 2000
NIOSH RTECS	CZ4550000	RTECS 2005
EPA Hazardous Waste	U072; D027	HSDB 2005
OHM/TADS	No data	
DOT/UN/NA/IMCO Shipping	UN 1592; IMO 6.1	HSDB 2005
HSDB	523	HSDB 2005
NCI	NCI-C54955	RTECS 2005

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

Table 4-2. Physical and Chemical Properties of 1,2-, 1,3-, and 1,4-Dichlorobenzene

Property	Value	Reference
Chemical name	1,2-Dichlorobenzene	Lide 2000
Molecular weight	147.00	Lide 2000
Color	Colorless to pale yellow	NIOSH 2005
Physical state	Liquid	Lewis 1997
Melting point	-16.7 °C	Lide 2000
Boiling point	180 °C	Lide 2000
Density at 20 °C	1.3059 g/mL	Lide 2000
Odor	Pleasant, aromatic	NIOSH 2005
Odor threshold:		
Water	0.01 mg/L	Verschueren 2001
Air	50 ppm (301 mg/m^3)	Verschueren 2001
Solubility:		
Water	156 mg/L at 25 °C	Banerjee et al. 1980
Organic solvents	Miscible with alcohol, ether, benzene	O'Neil 2001
Partition coefficients:		
Log octanol/water	3.43	Hansch et al. 1995
Log K_{oc}	2.51	Chiou et al. 1983
Vapor pressure at 25 °C	1.36 mm Hg	Daubert and Danner 1992
Henry's law constant at 25 °C	1.92x10^{-3} atm m^3/mol	Shiu and Mackay 1997
Autoignition temperature	640 °C	Krishnamurti 2001
Flashpoint	28 °C (closed cup)	Krishnamurti 2001
Flammability limits	No data	
Conversion factors	1 mg/m^3=0.116 ppm at 25 °C and 760 mm Hg; 1 ppm=6.01 mg/m^3 at 25 °C and 760 mm Hg	Verschueren 2001
Explosion limits	2–9% by volume in air	Leber and Bus 2001

Table 4-2. Physical and Chemical Properties of 1,2-, 1,3-, and 1,4-Dichlorobenzene

Property	Value	Reference
Chemical name	1,3-Dichlorobenzene	Lide 2000
Molecular weight	147.00	Lide 2000
Color	Colorless	Lewis 1997
Physical state	Liquid	Lewis 1997
Melting point	-24.8 °C	Lide 2000
Boiling point	173 °C	Lide 2000
Density at 20 °C	1.2884 g/mL	Lide 2000
Odor	No data	
Odor threshold:		
Water	0.02 mg/L	Verschueren 2001
Air	No data	
Solubility:		
Water	125 mg/L at 20 °C	Miller et al. 1984
Organic solvents	Soluble in alcohol, ether	O'Neil 2001
Partition coefficients:		
Log octanol/water	3.53	Hansch et al. 1995
Log K_{oc}	2.47	Chiou et al. 1983
Vapor pressure at 25 °C	2.15 mm Hg	Daubert and Danner 1992
Henry's law constant at 25 °C	2.8×10^{-3} atm m^3/mol	Staudinger and Roberts 1996
Autoignition temperature	>500 °C	Krishnamurti 2001
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	1 mg/ m^3=0.116 ppm at 25 °C and 760 mm Hg; 1 ppm=6.01 mg/m^3 at 25 °C and 760 mm Hg	HSDB 2005
Explosion limits	No data	

Table 4-2. Physical and Chemical Properties of 1,2-, 1,3-, and 1,4-Dichlorobenzene

Property	Value	Reference
Chemical name	1,4-Dichlorobenzene	Lide 2000
Molecular weight	147.00	Lide 2000
Color	Colorless or white	NIOSH 2005
Physical state	Solid	Lewis 1997
Melting point	52.7 °C	Lide 2000
Boiling point	174 °C	Lide 2000
Density at 20 °C	1.46 g/mL	O'Neil 2001
Odor	Mothball-like; penetrating	Lewis 1997; NIOSH 2005
Odor threshold:		
Water	0.011 mg/L	Amoore and Hautala 1983
Air	0.18 ppm (1.1 mg/m^3)	Amoore and Hautala 1983
Solubility:		
Water	80.0 mg/L	Yalkowsky and He 2003
Organic solvents	Soluble in alcohol, ether, benzene, chloroform, carbon disulfide	O'Neil 2001
Partition coefficients:		
Log octanol/water	3.44	Hansch et al. 1995
Log K_{oc}	2.44	Chiou et al. 1983
Vapor pressure at 25 °C	1.77 mm Hg	Daubert and Danner 1992
Henry's law constant at 25 °C	2.41x10^{-3} atm m^3/mol	Shiu and Mackay 1997
Autoignition temperature	>500 °C	Krishnamurti 2001
Flashpoint	67 °C (closed cup)	Krishnamurti 2001
Flammability limits	6.2–16%	Leber and Bus 2001
Conversion factors	1 ppm=6.01 mg/m^3 at 25 °C and 760 mm Hg; 1 mg/m^3=0.166 ppm at 25 °C and 760 mm Hg	Verschueren 2001
Explosion limits	No data	

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

5.1 PRODUCTION

Chlorinated benzenes are produced typically by reacting liquid benzene with gaseous chlorine in the presence of a catalyst at moderate temperature (unspecified) and atmospheric pressure (IARC 1999; Rossberg et al. 2002). This reaction yields a mixture of chlorobenzene isomers with varying degrees of chlorination. A maximum dichlorobenzene yield of 98% is obtainable in a batch process in which 2 moles of chlorine is used per mole of benzene (mass ratio approximately 1.8:1) in the presence of ferric chloride and sulfur monochloride (IARC 1999). 1,2- and 1,4- DCB are the major DCB isomers formed in this process, with 1,2:1,4 ratios dependant on the type of catalyst used (Table 5-1). 1,3-DCB is also formed, but in much smaller quantities (Krishnamurti 2001). The DCB isomers are typically separated by crystallization and distillation.

Production of 1,4-DCB in the United States has risen from approximately 15 million pounds (6,800 metric tons) in 1981 to approximately 72 million pounds (32,600 metric tons) in 1993 (IARC 1999). The production volume of 1,4-DCB reported by manufacturers in 1998 and 2002 was within the range of greater then 50 million pounds to 100 million pounds (>23,000–45,000 metric tons) (EPA 2002e). The historical rate of growth of this chemical from 1989–1998 was 1.1 percent per year (CMR 1999).

Production of 1,2-DCB in the United States fell from approximately 54 million pounds (24,700 metric tons) in 1975 to approximately 35 million pounds (15,800 metric tons) in 1993 (IARC 1999). The production volume of 1,2-DCB reported by manufacturers in 1998 was within the range of >50 million pounds to 100 million pounds (>23,000–45,000 metric tons) (EPA 2002e). In 2002, companies reported production within the range of <10 million pounds to 50 million pounds (<5,000–23,000 metric tons) (EPA 2002e). The historical rate of growth of this chemical from 1986–1995 was 0.7 percent per year (CMR 1996).

Production of 1,3-DCB in the United States was <1 million pounds (500 metric tons) in 1983 (IARC 1999). The production volume of this chemical reported by manufacturers was within 10 thousand pounds to 500 thousand pounds (5–200 metric tons) during reporting year 1986, >1 million pounds to 10 million pounds (500–5,000 metric tons) during reporting year 1990, and >500 thousand pounds to

Table 5-1. Influence of Catalysts on the Ratio 1,4-:1,2-Dichlorobenzene

Catalyst	Proportion of 1,4-dichlorobenzene (in percent) in the dichlorobenzene fraction	Ratio 1,4- : 1,2-dichlorobenzene
$MnCl_2 + H_2O$	ca. 50	1.03
$SbCl_5$		1.5
$FeCl_3$ or Fe	ca. 59	1.49–1.55
Metallosilicon organic compounds	61–74	1.56–2.8
$AlCl_3 – SnCl_4$		2.21
$AlCl_3 – TiCl_4$		2.25
Fe – S – PbO	ca. 70	
$FeCl_3$ – diethyl ether		2.38
Aluminum silicate-hexamethylene-diamine		2.7
$FeCl_3 – S_2Cl_2$	ca. 76	
$FeCl_3$ – divalent organic sulfur compounds	ca. 77	3.3
L-type zeolite	ca. 88	8.0
$TiCl_4$ (chlorinating agent is $FeCl_3$)		20–30

Source: Rossberg et al. 2002

1 million pounds (>200–500 metric tons) in reporting years 1994 and 1998 (EPA 2002e). Production volume data were not listed for reporting year 2002.

1,4-DCB is the most important of the three DCB isomers commercially (Elovaara 1998). However, the high 1,2- to 1,4-DCB ratio has traditionally created an isomer imbalance in the DCB market (CMR 1999). Decreasing demand for 1,2-DCB in recent years has resulted in an increased economic disadvantage for the companies producing these chemicals.

1,4-DCB and 1,2-DCB are currently produced by 2 U.S. companies at 2 different locations: Solutia Inc., in Sauget, Illinois and PPG Industries, Inc., in Natrium, West Virginia (SRI 2005). Current annual 1,4-DCB production capacity for Solutia Inc. and PPG Industries, Inc. are 39 and 40 million pounds (17,700 and 18,100 metric tons), respectively (SRI 2005). Total annual production capacity for this isomer has fluctuated during the last 2 decades. The annual production capacity was 119 (54,000), 132 (59,900), 371 (168,000), 144 (65,000), 145(66,000), 154(70,000), and 79 (35,800) million pounds (metric tons) in 1983, 1988, 1995, 1997, 1999, 2001, and 2003 respectively (SRI 1984, 1988, 1995, 1997, 1999, 2001, 2003). Current annual 1,2-DCB production capacity for Solutia and PPG are 13 and 20 million pounds (5,900 and 9,000 metric tons), respectively (SRI 2005). The annual production capacity for the 1,2- isomer was 78 (35,000), 81 (37,000), 81 (37,000), 76 (34,000), 80 (36,000), 83 (38,000), and 33 (15,000) million pounds (metric tons) in 1983, 1988, 1995, 1997, 1999, 2001, and 2003 respectively (SRI 1984, 1988, 1995, 1997, 1999, 2001, 2003).

Tables 5-2, 5-3, and 5-4 list the facilities in each state that manufacture or process 1,2-, 1,3-, and 1,4-DCB, respectively. These tables give the intended use and the range of maximum amounts of each DCB isomer that are stored on site. The data listed in Tables 5-2 through 5-4 are derived from the Toxics Release Inventory (TRI03 2005). Only certain types of facilities were required to report (EPA 1997b). Therefore, this is not an exhaustive list.

5.2 IMPORT/EXPORT

In 1978, about 1.09×10^4 kg (24,030 pounds) of 1,4-DCB were imported into the United States (HSDB 2005; NTP 1989). Import volumes of 1,4-DCB were 867,441 kg (1.9 million pounds), 1,113,676 kg (2.5 million pounds), 996,649 kg (2.2 million pounds), 3,283,759 kg (7.2 million pounds), and 3,019,233 kg (6.7 million pounds) for 1990, 1991, 1992, 1993, and 1994, respectively. U.S.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	3	1,000	999,999	6, 11, 12
AR	12	100	49,999,999	2, 3, 6, 7, 10, 12
AZ	1	1000	9,999	11
CA	15	100	9,999,999	2, 3, 7, 8, 9, 11, 12
CO	1	1,000	9,999	7
CT	2	1,000	99,999	12
DE	6	1,000	9,999,999	1, 3, 4, 6, 7, 9
FL	2	10,000	99,999	7, 11
GA	3	1,000	99,999	7, 8
IL	3	1,000	9,999,999	1, 4, 12
IN	8	100	999,999	2, 3, 7, 10, 12
KS	3	100	99,999	12
KY	2	10,000	999,999	1, 3, 6
LA	12	100	999,999	1, 5, 6, 10, 12
MA	8	100	999,999	7, 10, 11, 12
MI	4	0	9,999	7, 8, 9, 12
MN	1	1,000	9,999	12
MO	6	100	99,999,999	7, 9, 12
MS	5	0	999,999	1, 3, 9, 11, 12
NC	12	100	999,999	2, 3, 6, 7, 10, 11, 12
NE	2	10,000	999,999	12
NH	1	0	99	12
NJ	22	1,000	9,999,999	2, 3, 6, 7, 8, 9, 10, 12, 14
NY	8	1,000	999,999	10, 11, 12
OH	8	1,000	9,999,999	3, 7, 9, 10, 11, 12
OK	1	1,000	9,999	12
OR	2	10,000	99,999	8, 12
PA	9	0	999,999	3, 7, 10, 11, 12
RI	4	1,000	99,999	7, 8, 10
SC	6	100	999,999	6, 10, 11, 12
TN	3	10,000	999,999	10, 11
TX	31	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
VA	2	10,000	999,999	12
WI	3	10,000	999,999	9, 10
WV	6	100,000	49,999,999	1, 4, 10, 11

Source: TRI03 2005 (Data are from 2003)

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

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

Table 5-3. Facilities that Produce, Process, or Use 1,3-Dichlorobenzene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	1,000	9,999	12
CA	1	100	999	12
DE	7	100	9,999,999	1, 3, 4, 5, 6, 13
IL	5	1,000	9,999,999	1, 4, 5, 12, 13
IN	1	100	999	12
KY	1	10,000	99,999	1, 3, 6
LA	4	1,000	999,999	1, 5
MI	2	100,000	999,999	2, 3, 6
MO	3	100	99,999	6, 12
MS	1	100	999	12
NJ	3	100	999,999	3, 6, 10, 12
OH	2	1,000	99,999	12
SC	1	10,000	99,999	6
TX	7	0	99,999	1, 5, 11, 12, 13
WV	3	100,000	9,999,999	1, 4, 5, 13

Source: TRI03 2005 (Data are from 2003)

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

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

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	6	1,000	99,999	1, 2, 6, 7, 12, 13
CA	2	100	999	3, 4, 9, 12
DE	2	1,000,000	49,999,999	1, 3, 4, 6
FL	4	10,000	99,999	4, 7, 9
GA	9	1,000	999,999	7, 8, 9, 12
IL	8	0	9,999,999	1, 2, 3, 4, 7, 9, 11, 12, 14
IN	6	100	99,999	7, 8, 11, 12
KS	8	100	999,999	7, 9, 12
KY	3	1,000	99,999	2, 4, 12
LA	8	0	999,999	1, 5, 6, 13
MA	5	1,000	999,999	2, 3, 7, 11
MI	2	1,000	99,999	2, 5
MO	4	100	999,999	1, 5, 8, 12
NC	5	100	999,999	2, 3, 6, 11, 12
NE	1	10,000	99,999	12
NJ	12	1,000	999,999	2, 3, 4, 7, 8, 9, 12
NY	1	100	999	2, 4
OH	13	1,000	999,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12
OK	4	1,000	99,999	2, 3, 6, 8
PA	6	100	99,999	3, 7, 9, 10, 11, 12
SC	2	10,000	99,999	6, 12
TX	12	0	49,999,999	1, 2, 3, 5, 6, 7, 12, 13
UT	1	1,000	9,999	12
VA	1	1,000	9,999	12
WV	1	1,000,000	9,999,999	1, 4

Source: TRI03 2005 (Data are from 2003)

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

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

imports of 1,2-DCB were 6,300 kg in 1972 and 1,230,000 kg in 1975 (HSDB 2005). U.S. imports of 1,3-DCB were 56,600 kg in 1983 (HSDB 2005). More recent import data for the DCB isomers were not available.

In 1972, U.S. exports of 1,4-DCB were reported to be 4.5×10^6 kg (9.9 million pounds) (HSDB 2005). Exports of 1,4-DCB have expanded through the 1980s at about 1–2% per year due to the growth in production of polyphenylene sulfide (PPS) resin overseas (HSDB 2005; NTP 1989). In 1990, the United States exported about 25% (about 33 million pounds) of its 1,4-DCB production volume (CMR 1990). Export volumes of 1,4-DCB were 11,925,179 kg (24.1 million pounds), 11,185,034 kg (24.7 million pounds), 10,651,337 kg (23.5 million pounds), 13,390,545 kg (29.5 million pounds), and 11,078,150 kg (24.4 million pounds) for 1990, 1991, 1992, 1993, and 1994, respectively. 1,4-DCB exports during 1994–1997 averaged 25 million pounds (11,000 metric tons) (CMR 1999). U.S. exports of 1,2-DCB averaged 14 million pounds (6,000 metric tons) per year during 1991–1995 (CMR 1996). Export data for 1,3-DCB were not available.

Based on a 1993 production volume value of 72 million pounds (32,600 metric tons), an import value of 7 million pounds (3,000 metric tons), and an export value of 30 million pounds (14,000 metric tons), the total amount of 1,4-DCB available for use in U.S. commerce in 1993 was 49 million pounds (22,000 metric tons). Based on a 1993 production volume value of 35 million pounds (15,800 metric tons) and an export value of 14 million pounds (6,000 metric tons), the total amount of 1,2-DCB remaining in the United States in 1993 was 21 million pounds (10,000 metric tons) assuming that imports of this chemical during that year were negligible. It should be noted, however, that not all of the 1,2-DCB that is produced is expected to be available for use since large quantities of this chemical are more likely to be disposed of when it is produced as a byproduct in the production of 1,4-DCB. Although reported export values for 1,2- and 1,4-DCB show that considerable amounts of these chemicals have been sent to other countries in previous years, the production volumes for these chemicals have been consistently higher suggesting that more than half of the amounts produced each year have remained in the United States.

5.3 USE

For the past 20 years, 1,4-DCB has been used principally (25–55% of all uses) as a space deodorant for toilets and refuse containers, and as a fumigant for control of moths, molds, and mildews. In recent years, the use of 1,4-DCB in the production of polyphenylene sulfide (PPS) resin has increased steadily (25–

50% of its total use). 1,4-DCB is also used as an intermediate in the production of other chemicals such as 1,2,4-trichlorobenzene (approximately 10%). Minor uses of 1,4-DCB include its use in the control of certain tree-boring insects and ants, and in the control of blue mold in tobacco seed beds (CMR 1999; HSDB 2005).

1,2-DCB is used primarily as a precursor to 3,4-dichloroaniline herbicides. Other uses of 1,2-dichloro-aniline include its use as a solvent, in the synthesis of dyes, and in odor control products (CMR 1996; HSDB 2005).

1,3-DCB has been used in the production of herbicides and insecticides as well as in the production of pharmaceuticals and dyes (IARC 1999).

5.4 DISPOSAL

Wastes containing DCBs are considered hazardous if they meet certain criteria specified by law. Hazardous wastes are subject to the handling, transport, treatment, storage, and disposal regulations as promulgated under the Resource Conservation and Recovery Act (HSDB 2005; IRPTC 1985). Regulations governing the treatment and disposal of wastes containing DCBs are detailed in Chapter 8.

Incineration by appropriate means is the recommended method for the disposal of waste 1,4-DCB (HSDB 2005). 1,4-DCB may be disposed of by making packages of the chemical in paper or other disposable material and burning in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device or by dissolving the chemical in a flammable solvent (such as alcohol) and atomizing in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device (IRPTC 1985). Halogenated compounds may be disposed of by incineration provided they are blended with other compatible wastes or fuels so that the composite contains <30% halogens. Liquid injection, rotary kiln, and fluidized bed incinerators are typically used to destroy liquid halogenated wastes. Temperatures of at least 2,000–2,200 °F are necessary. Residence times of seconds are required for liquids and gases, while hours are required for solids (HSDB 2005). 1,2-DCB is produced in large quantities as a byproduct during the production of 1,4-DCB. Unused supplies may be disposed of or released directly into the environment.

No data were located regarding historic disposal trends or the amounts of 1,2-, 1,3-, or 1,4-DCB disposed of by different means.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,2-, 1,3- and 1,4-Dichlorobenzene (DCB) have been identified in at least 281, 175, and 330, respectively, of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL), respectively (HazDat 2005). However, the number of sites evaluated for these DCB isomers is not known. The frequency of these sites can be seen in Figures 6-1, 6-2, and 6-3. Of these sites, all are located within the United States.

1,4-DCB is a widely used chemical that enters the environment primarily as releases to air during its use as a space deodorant, toilet deodorizer, and moth repellant. 1,2- and 1,3-DCB are expected to be released to the environment during their use in herbicide production or during the use of other products containing these isomers. However, 1,2- and 1,3-DCB are used much less than the 1,4-isomer. Disposal of 1,2-DCB, which is produced as a by-product in the manufacture of 1,4-DCB, may be a significant pathway by which 1,2-DCB is released into the environment. DCBs are not known to occur naturally in the environment and are solely produced by commercial, industrial, and consumer activities.

DCBs are degraded in the atmosphere by reaction with hydroxyl radicals, with a calculated atmospheric lifetime of 14-31 days (Atkinson 1989; Howard 1989). DCBs will exist predominantly in the vapor-phase in the atmosphere, and their detection in rainwater suggests that atmospheric removal via washout is possible (Ligocki et al. 1985). Depending on soil type, DCBs are expected to be moderately mobile in soil. They are also expected to volatilize from surface water and soil surfaces to the atmosphere. Volatilization, sorption, biodegradation, and bioaccumulation are likely to be competing processes, with the dominant fate being determined by local environmental conditions.

The principal route of exposure to DCBs for the general population (including children) is via inhalation, with average daily adult intakes from ambient air estimated at about 35 μg for 1,4-DCB, 1.8 μg for 1,2-DCB, and 0.8 μg for 1,3-DCB (EPA 1985a; Singh et al. 1981a, 1981b). Recent data suggest that exposure to 1,4-DCB from indoor air may be an order of magnitude higher than exposures from ambient outdoor air (Wallace et al. 1986b). Indoor inhalation exposure to 1,2- or 1,3-DCB is not expected to be as high as 1,4-DCB since these substances are not used in household and consumer products to the extent that 1,4-DCB is. Consumer contact with 1,4-DCB associated with its use in moth repellant crystals and

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

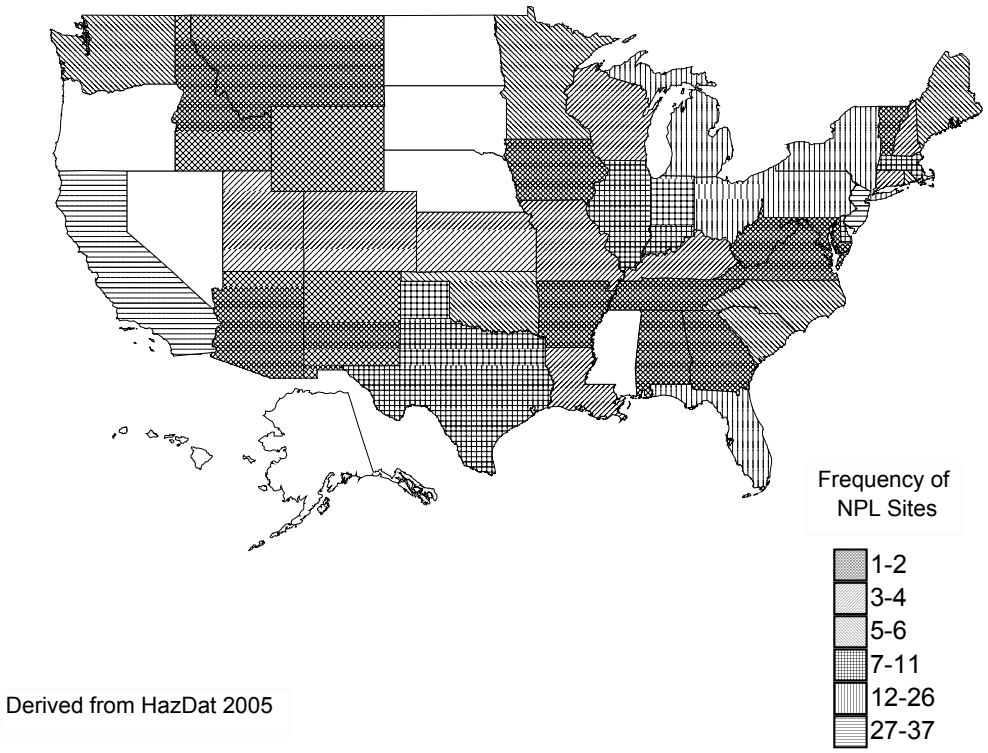


Figure 6-2. Frequency of NPL Sites with 1,3-Dichlorobenzene Contamination

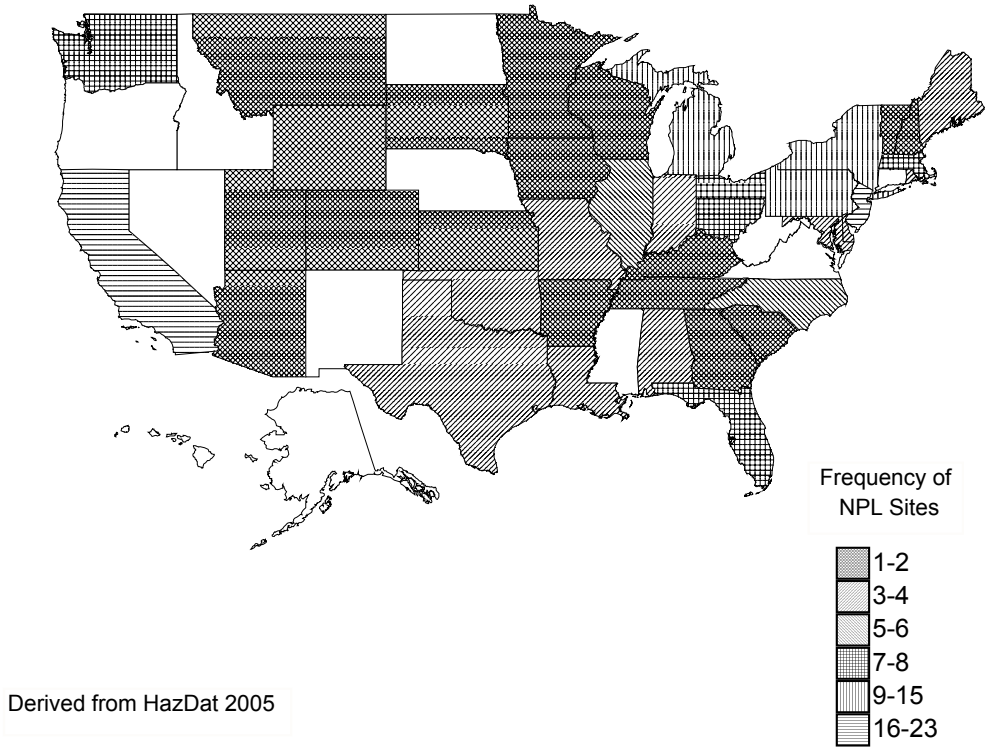
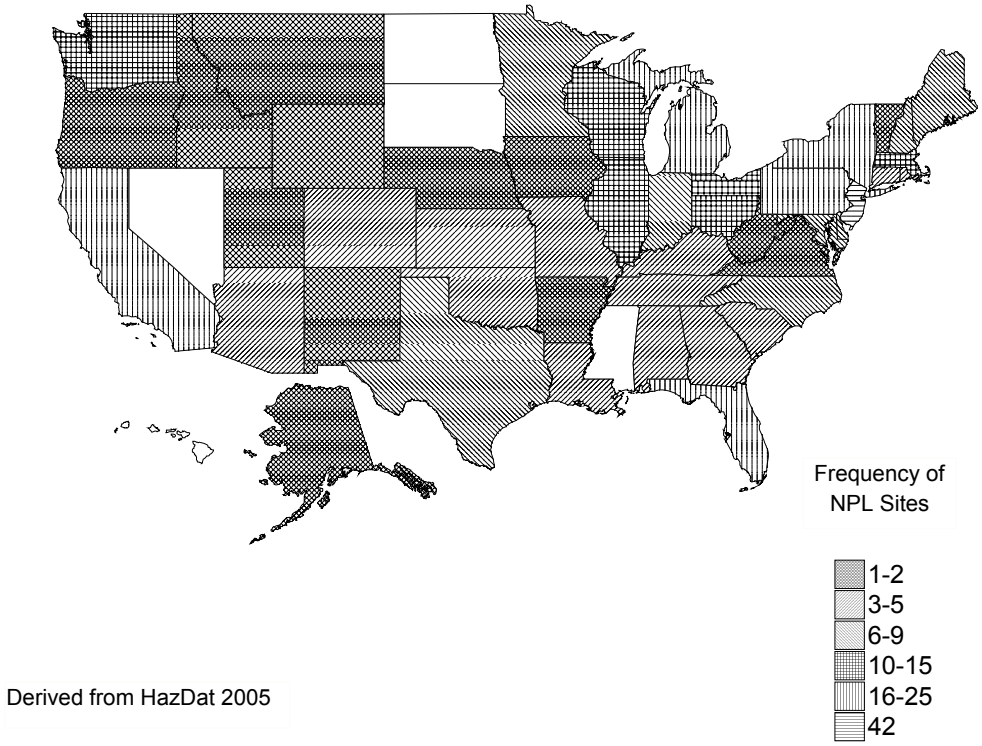


Figure 6-3. Frequency of NPL Sites with 1,4-Dichlorobenzene Contamination



toilet deodorizers is the most frequent means of exposure to this compound in the home (Wallace et al. 1986b, 1989). DCBs have been detected in various types of foods and drinking water, although generally in low concentrations (Heikes et al. 1995; IARC 1999; Page and Lacroix 1995; Young and Heesen 1978; Young et al. 1980). DCB exposure through these pathways is not expected to be important. Children may be accidentally exposed to 1,4-DCB if they eat moth balls or toilet deodorizers. Occupational exposure is primarily through inhalation or dermal contact with DCBs, with the highest exposure resulting from production or processing of these chemicals (IARC 1999).

6.2 RELEASES TO THE ENVIRONMENT

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

According to the TRI, in 2003, a total of 92,973 pounds (42 metric tons) of 1,2-DCB was released to the environment from 39 large processing facilities (TRI03 2005). Table 6-1 lists amounts released from these facilities. Of this total, an estimated 87,443 pounds (40 metric tons) were released to air, 1,240 pounds (0.6 metric tons) were released to water, 1,784 pounds (0.8 metric tons) were released to land, and 2,500 pounds (1 metric ton) were released via underground injection. The total amount of 1,2-DCB released on-site was estimated as 91,868 pounds (42 metric tons). The total amount released off-site was estimated as 1,104 pounds (0.5 metric tons) (TRI03 2005).

According to the TRI, in 2003, a total of 1,966 pounds (0.9 metric tons) of 1,3-DCB was released to the environment from eight large processing facilities (TRI03 2005). Table 6-2 lists amounts released from

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dichlorobenzene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	4	78	No data	0	0	0	78	0	78
CA	1	640	No data	0	0	0	640	0	640
IL	2	8,961	No data	0	5	5	8,961	10	8,971
IN	1	9,700	750	0	0	0	10,450	0	10,450
KS	1	2	No data	0	0	0	2	0	2
KY	1	3	0	0	0	0	3	0	3
LA	2	7,800	8	2,500	110	0	10,308	110	10,418
MA	1	360	No data	0	0	0	360	0	360
MS	2	510	No data	0	0	0	510	0	510
NC	2	1,250	No data	0	0	0	1,250	0	1,250
NE	1	5	No data	0	0	0	5	0	5
NJ	2	652	13	0	1,267	0	1,225	707	1,932
NY	1	5	No data	0	0	0	5	0	5
OH	1	5	5	0	255	0	10	255	265
PA	2	10	No data	0	0	0	10	0	10
RI	1	2,068	4	0	22	0	2,072	22	2,094
SC	2	9,707	5	0	0	0	9,712	0	9,712
TN	1	No data	No data	No data	No data	No data	No data	0	0
TX	9	5,137	3	0	110	0	5,251	0	5,251
WV	2	40,550	452	0	15	0	41,017	0	41,017
Total	39	87,443	1,240	2,500	1,784	5	91,868	1,104	92,973

Source: TRI03 2005 (Data are from 2003)

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

RF = reporting facilities; UI = underground injection

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,3-Dichlorobenzene[a]

		Reported amounts released in pounds per year[b]					
					Total release		
State[c]	RF[d]	Air[e]	Water[f]	Land[h]	On-site[j]	Off-site[k]	On- and off-site
AR	1	0	No data	0	0	0	0
IL	1	451	No data	0	451	0	451
KY	1	2	0	0	2	0	2
OH	1	5	5	255	10	255	265
SC	1	182	5	0	187	0	187
TX	2	43	3	0	47	0	47
WV	1	664	350	0	1,014	0	1,014
Total	8	1,347	363	255	1,711	255	1,966

Source: TRI03 2005 (Data are from 2003)

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

RF = reporting facilities; UI = underground injection

these facilities. Of this total, an estimated 1,347 pounds (0.6 metric tons) were released to air, 363 pounds (0.2 metric tons) were released to water, 255 pounds (0.1 metric tons) were released to land, and 0 pounds were released via underground injection. The total amount of 1,3-DCB released on-site was estimated as 1,711 pounds (0.8 metric tons). The total amount released off-site was estimated as 255 pounds (0.1 metric tons) (TRI03 2005).

According to the TRI, in 2003, a total of 96,993 pounds (44 metric tons) of 1,4-DCB was released to the environment from 21 large processing facilities (TRI03 2005). Table 6-3 lists amounts released from these facilities. Of this total, an estimated 85,463 pounds (39 metric tons) were released to air, 815 pounds (0.4 metric tons) were released to water, 270 pounds (0.1 metric tons) were released to land, and 10,408 pounds (5 metric tons) were released via underground injection. The total amount of 1,4-DCB released on-site was estimated as 96,696 pounds (44 metric tons). The total amount released off-site was estimated as 297 pounds (0.1 metric tons) (TRI03 2005). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

1,2-, 1,3-, and 1,4-DCB have been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 281, 175, and 330 of the 1,662 NPL hazardous waste sites, respectively (HazDat 2005). The number of these sites located in each state can be seen in Figures 6-1, 6-2, and 6-3.

Quantitative information on releases of DCBs to specific environmental media is discussed below.

6.2.1 Air

According to the TRI, estimated releases of 1,2-DCB of 87,443 pounds (40 metric tons) to the air from 39 large processing facilities accounted for about 93% of the total TRI environmental releases in 2003 (TRI03 2005). Table 6-1 lists amounts of 1,2-DCB released from these facilities. Estimated releases of 1,3-DCB of 1,347 pounds (0.6 metric tons) to the air from eight large processing facilities accounted for about 69% of the total TRI environmental releases in 2003 (TRI03 2005). Table 6-2 lists amounts of 1,3-DCB released from these facilities. Estimated releases of 1,4-DCB of 85,463 pounds (38 metric tons) to the air from 20 large processing facilities accounted for about 88% of the total TRI environmental releases in 2003 (TRI03 2005). Table 6-3 lists amounts of 1,4-DCB released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997b). Therefore, this is not an exhaustive list.

Table 6-3. Releases to the Environment from Facilities that Produce, Process, or Use 1,4-Dichlorobenzene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	2	3	No data	0	0	0	3	0	3
GA	1	No data	No data	No data	No data	No data	No data	0	0
IL	2	25,111	5	0	0	0	25,116	0	25,116
KS	2	2,105	No data	0	5	0	2,105	5	2,110
KY	1	2	No data	0	0	0	2	0	2
MO	1	766	No data	0	0	0	766	0	766
NC	1	11,515	6	0	0	0	11,521	0	11,521
OH	2	1,385	5	0	255	0	1,390	255	1,645
OK	1	569	No data	0	0	0	569	0	569
PA	1	10	No data	0	0	0	10	0	10
SC	1	No data	No data	No data	No data	No data	No data	0	0
TX	3	14,725	3	10,408	10	0	25,146	0	25,146
UT	2	2	No data	0	0	37	2	37	39
WV	1	29,270	796	0	0	0	30,066	0	30,066
Total	21	85,463	815	10,408	270	37	96,696	297	96,993

Source: TRI03 2005 (Data are from 2003)

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

RF = reporting facilities; UI = underground injection

Because 1,4-DCB is a volatile substance that sublimes at room temperature, most environmental releases are to the atmosphere. In 1972, 70–90% of the annual U.S. production of 1,4-DCB was estimated to have been released into the atmosphere primarily as a result of its use in toilet bowl and garbage deodorants, and its use in moth control as a fumigant (IARC 1982). It has been estimated that about 40% of the domestic use of 1,4-DCB is for space deodorants moth repellents (CMR 1999). Assuming that 90% of the space deodorants and all of the moth repellents are released to the atmosphere (EPA 1981a), and using current production data (50–100 million pounds or 23,000–45,000 metric tons) (EPA 2002e), about 20–40 million pounds (9,000–18,000 metric tons) of 1,4-DCB were released to the air in 1994 from these sources. 1,4-DCB may also be emitted to air from other sources, such as hazardous waste sites (EPA 1981a), during its use as a fumigant (EPA 1981a), or from emissions from waste incinerator facilities (Jay and Stieglitz 1995). These emissions are likely to be a minor contribution to the total atmospheric loading of 1,4-DCB, but may be locally important. There are no known natural sources of 1,4-DCB (IARC 1999).

1,2- and 1,3-DCB, which are volatile liquids at room temperature, are also expected to be released primarily to air. Unlike 1,4-DCB, however, the 1,2- and 1,3- isomers are not widely used in household or consumer products and thus are not released into the air of homes and buildings to the extent of the 1,4-isomer. 1,2- and 1,3-DCB are expected to be released to the air during their use in herbicide production, during the use of other products containing these isomers, or from air emissions at hazardous waste sites and incinerator facilities. Another significant source for the release of 1,2-DCB to air may be from the disposal of this substance when it is produced as a by-product in the production of 1,4-DCB. There are no known natural sources of 1,2- or 1,3-DCB (IARC 1999).

The concentrations of 1,2-, 1,3-, and 1,4-DCB in the emissions of a municipal waste incineration plant were 2.32×10^{-6}, 2.44×10^{-6}, and 5.92×10^{-5} ppm, respectively (Jay and Stieglitz 1995). DCBs were detected in emissions from municipal solid waste composting facilities at concentrations of 1.16×10^{-4} ppm for 1,2-DCB, 2.32×10^{-4} ppm for 1,3-DCB, and 1.04×10^{-2} ppm for 1,4-DCB (Eitzer 1995). Garcia et al. (1992) measured 1,4-DCB concentrations ranging from 3.48×10^{-5} to 4.99×10^{-4} ppm in the emissions of coal-fired power stations. 1,2-DCB was detected in landfill gas at the Fresh Kills municipal solid waste landfill in New York City with a mean concentration of 2.17 ppm (Eklund et al. 1998).

1,2-DCB has been identified in air samples collected at 15 of the 281 NPL hazardous waste sites, respectively, where it has been detected in at least one environmental medium (HazDat 2005). 1,3-DCB has been identified in air samples collected at 9 of the 175 NPL hazardous waste sites where it has been

detected in some environmental media (HazDat 2005). 1,4-DCB has been identified in air samples collected at 23 of the 330 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 2005).

6.2.2 Water

According to the TRI, the estimated releases of 1,2-DCB of 1,240 pounds (0.6 metric tons) to water from 39 large processing facilities accounted for 1% of the total TRI environmental releases in 2003 (TRI03 2005). An additional 1,104 pounds (0.5 metric tons) (1% of total TRI environmental releases) were released off-site, which includes release to publicly owned treatment works (POTWs). Table 6-1 lists amounts of 1,2-DCB released from these facilities. Estimated releases of 1,3-DCB of 363 pounds (0.2 metric tons) to water from eight large processing facilities accounted for 18% of the total TRI environmental releases in 2003 (TRI03 2005). An additional 255 pounds (0.1 metric tons) (13% of total TRI environmental releases) were released off-site, which includes release to POTWs. Table 6-2 lists amounts of 1,3-DCB released from these facilities. Estimated releases of 1,4-DCB of 815 pounds (0.4 metric tons) to water from 21 large processing facilities accounted for 0.8% of the total TRI environmental releases in 2003 (TRI03 2005). An additional 297 pounds (0.1 metric tons) (0.3% of total TRI environmental releases) were released off-site, which includes release to POTWs. Table 6-3 lists amounts of 1,4-DCB released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997b). Therefore, this is not an exhaustive list.

Less than 1% of environmental releases of 1,4-DCB are to surface water (EPA 1981a). The main route for the release of this substance to surface water is expected to be through its extensive use in urinal deodorant blocks (IARC 1999). 1,2-DCB is released into industrial waste water during its production and use. 1,2-DCB might also be released into waste water during the disposal of this substance when it is produced as a by-product in the production of 1,4-DCB. Data concerning the release of 1,3-DCB to water are lacking. Release of this substance to water may occur during its production, use, or disposal. DCBs have been identified in industrial and municipal waste waters from several sources, at concentrations ranging from <3 to >900 ppb (Oliver and Nichol 1982a; Perry et al. 1979; Young and Heesen 1978; Young et al. 1980, 1981). 1,2- and 1,4-DCB were both detected in 1% of 84 possible detections in influent samples from the New York City municipal waste water treatment system at concentrations of 22 and 4 ppb, respectively (Stubin et al. 1996). 1,2-DCB was detected in 2% while 1,4-DCB was detected in 1% of 84 possible detections in effluent samples at concentrations of 4–6 and 3 ppb,

respectively. The concentrations of 1,2-DCB were higher than those of 1,4-DCB, which is contrary to what is expected for these substances in residential and domestic waste water. However, no explanation was offered for this. The concentration of 1,4-DCB in the effluent of the North Regional Wastewater Treatment Plant in Broward County, Florida was approximately 1.2 ppb (Tansel and Eyma 1999). 1,4-DCB was detected above "standard levels" (unspecified) in sediment at the end of the Macaulay Point and Clover Point waste water outfalls off the coast of Vancouver, British Columbia (Taylor et al. 1998).

DCB (unspecified isomers) has been reported in the leachate from industrial and municipal landfills at concentrations from 0.007 to 0.52 ppm (7–520 ppb) (Brown and Donnelly 1988). Eganhouse et al. (2001) identified 1,4-DCB at a concentration of 0.1–5.6 ppb in a landfill leachate plume in groundwater from a municipal landfill located in Norman, Oklahoma. DCBs have also been detected in wetland-treated leachate water at a municipal solid waste landfill in central Florida (Chen and Zoltek 1995). Groundwater samples contained 1,2-DCB at concentrations of 0.09–1.56 ppb, 1,3-DCB at concentrations of 0.08–8.95 ppb, and 1,4-DCB at concentrations of 0.08–10.71 ppb. Hallbourg et al. (1992) detected DCB (unspecified isomers) in groundwater at several landfill sites in Orange County, Florida. These authors reported mean concentrations of DCBs of 0.37–21.2, 6–46.4, and <1–7.4 ppb at the Orange County Landfill, Alachua County Southwest Landfill, and the Alachua County Northeast Landfill, respectively. In their study, DCB was one of the 10 most frequently detected volatile organic compounds (VOCs). Plumb (1991) also reported 1,2-, 1,3-, and 1,4-DCB in groundwater samples collected at 36, 16, and 34 of 479 hazardous waste sites, respectively.

1,4-DCB was monitored for, but not detected, in 86 samples of urban storm water runoff in the National Urban Runoff Program (Cole et al. 1984). DCBs were detected in four rivers (Aire, Calder, Don, and Trent) that drain an industrial catchment from the United Kingdom into the North Sea (Meharg et al. 2000). Annual fluxes in these rivers ranged from 1.37 to 32.91 kg/year for 1,2-DCB, 0.12 to 9.33 kg/year for 1,3-DCB, and 6.80 to 28.96 kg/year for 1,4-DCB.

1,2-DCB has been identified in surface water and groundwater samples collected at 29 and 186 of the 281 NPL hazardous waste sites, respectively, where it was detected in at least one environmental medium (HazDat 2005). 1,3-DCB has been identified in surface water and groundwater samples collected at 13 and 107 of the 175 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2005). 1,4-DCB has been identified in surface water and groundwater samples collected at 31 and 213 of the 330 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2005).

6.2.3 Soil

According to the TRI, releases of 1,2-DCB to land of 1,784 pounds (0.8 metric tons) from 39 large processing facilities accounted for 2% of total TRI environmental releases in 2003 (TRI03 2005). An estimated 2,500 pounds (1 metric ton) (3% of total TRI environmental releases) were released via underground injection. Table 6-1 lists amounts of 1,2-DCB released from these facilities. Releases of 1,3-DCB of 255 pounds (0.1 metric tons) to the land from eight large processing facilities accounted for 13% of total TRI environmental releases in 2003 (TRI03 2005). Table 6-2 lists amounts of 1,3-DCB released from these facilities. There were no releases of 1,3-DCB to the underground in 2003 as shown in Table 6-2. Releases of 1,4-DCB of 270 pounds (0.1 metric tons) to the land from 21 large processing facilities accounted for 0.2% of total TRI environmental releases in 2003 (TRI03 2005). In addition, an estimated 10,408 pounds (0.5 metric tons) (11% of total environmental releases) were released via underground injection. Table 6-3 lists amounts of 1,4-DCB released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997b). Therefore, this is not an exhaustive list.

The principal sources of 1,4-DCB release to land are disposal of industrial waste in landfills, application of sewage sludge containing 1,4-DCB to agricultural land, and atmospheric deposition (Wang and Jones 1994b; Wang et al. 1995). Municipal wastes may include unused space deodorants and moth repellents containing 1,4-DCB, but these releases are not expected to be significant (EPA 1981a). A survey of 204 sewage sludges conducted in Michigan that analyzed for 73 organic compounds reported a concentration range of 0.04–633 mg/kg dry weight (ppm) for 1,4-DCB and mean and median concentrations of 12.0 and 2.02 ppm, respectively (Jacobs and Zabik 1983). 1,4-DCB from this source may be released to soils during land applications of sludge to agricultural soils. A similar survey of sewage sludges in England found 1,4-DCB ranging from 561 to 2,320 μg/kg (0.561–2.32 ppm wet weight) in all 12 of the samples tested (Wang and Jones 1994b). Wang et al. (1995) reported, however, that 1,4-DCB concentrations increased during the 1960s in both plots receiving sewage sludge applications and in control soil plots. The authors concluded that atmospheric deposition during the 1960s in particular, which corresponded to a period of increased production of many organochlorine compounds, was a likely source. 1,2-DCB was detected in all 12 sewage sludge samples at concentrations ranging from 71.3 to 4,110 μg/kg (ppb) dry weight (3.57–152 ppb wet weight). The concentrations of 1,2-DCB in industrial sewage sludge was considerably higher than in urban sewage

sludge. 1,3-DCB was detected in 9 out of 12 sewage sludge samples at concentrations ranging from below the detection limit to 467 μg/kg (ppb) dry weight (below the detection limit–13.5 ppb wet weight).

1,2-DCB is produced in large quantities as a by-product in the production of 1,4-DCB. The TRI data for this substance suggest that 1,2-DCB may be released into the ground during the disposal of unused supplies. Data concerning the release of 1,3-DCB to soil were lacking. Based on TRI data, the production volume of these chemicals, and their uses, releases of this isomer to soil are expected to be minor compared to the other DCB isomers.

1,2-DCB has been identified in soil and sediment samples collected at 111 and 37 of the 281 NPL hazardous waste sites, respectively, where it was detected in at least one environmental medium (HazDat 2005). 1,3-DCB has been identified in soil and sediment samples collected at 64 and 25 of the 175 NPL hazardous waste sites, respectively, where it was detected in at least one environmental medium (HazDat 2005). 1,4-DCB has been identified in soil and sediment samples collected at 112 and 52 of the 330 NPL hazardous waste sites, respectively, where it was detected in at least one environmental medium (HazDat 2005).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Whereas 1,2- and 1,3-DCB are liquids at room temperature, 1,4-DCB is a solid that sublimes readily. Sublimation rates of 1,4-DCB from consumer products were measured at 1.6×10^{-3} to 4.6×10^{-3} g/minute at temperatures ranging from 21 to 24 °C during a 19-day test period (Scuderi 1986). DCBs tend to volatilize to the atmosphere from soil and water at a relatively rapid rate. The estimated volatilization half-life for these chemicals was 4 hours in a model river and 120 hours from a model lake (HSDB 2005). The reported volatilization half-lives for 1,4-DCB measured in coastal seawater ranged from 10 to 18 days (Wakeham et al. 1983). 1,2-DCB (100 ppm) and 1,4-DCB (300 ppm) both volatilized completely from nonaerated distilled water in <3 days and from aerated distilled water in <4 hours (Garrison and Hill 1972). Volatilization from surface soil may be an important transport mechanism for DCBs (Wang and Jones 1994a), but adsorption to soil particulates may inhibit volatilization (Wilson et al. 1981).

Since DCBs are slightly soluble in water (80.0–156 mg/L) (Banerjee et al. 1980; Miller et al. 1984; Yalkowsky and He 2003), partitioning to clouds, rain, or surface water may occur. Henry's Law constant values ranging from 1.74×10^{-3} to 2.63×10^{-3} atm-m^3/mol at 25 °C (Shiu and Mackay 1997; Staudinger and Roberts 1996) indicate that partitioning from air to water is likely to be minor relative to the reverse process of volatilization of the compound from water to air. However, DCBs have been detected in rainwater and snow (Laniewski et al. 1998, 1999; Ligocki et al. 1985). The concentration of 1,4-DCB detected in 6 of 7 rainwater samples collected in Portland, Oregon, ranged from 3 to 7 ppt (ng/L), while the concentration of 1,2-DCB detected in 5 out of 7 rainwater samples ranged from 0.13 to 0.62 ppt (Ligocki et al. 1985). DCBs have been detected in surficial snow from Antarctica (Laniewski et al. 1998), which suggests that these substances can be transported over long distances through the atmosphere.

Based on measured soil organic carbon partition coefficient (K_{oc}) values, which range from 275 to 1,833 in different soils (Bahnick and Doucette 1988; Chiou et al. 1983; Newsom 1985; Schwartzenbach and Westall 1981; Wilson et al. 1981), DCBs are expected to sorb moderately to soils and sediments. Sorption is primarily to the soil organic phase (Chiou et al. 1983) and, therefore, depends on the organic content of the soil. However, sorption is likely to be reversible; therefore, DCBs may leach from hazardous waste sites and be transported to groundwater, or may migrate from surface water through the soil to groundwater (Newsom 1985; Schwartzenbach and Westall 1981). In a sandy soil with low organic matter, 26–49% of 1,4-DCB percolated through the soil to a depth of 140 cm (Wilson et al. 1981).

DCBs are expected to bioconcentrate in aquatic organisms. High log octanol-water partition coefficient (log K_{ow}) values of 3.43–3.53 (Hansch et al. 1995) also suggest that DCBs have a moderate to high potential for bioaccumulation. A calculated bioconcentration factor (BCF) of 267 was reported for the fathead minnow *(Pimephales promelas)* (ASTER 1995). Measured mean BCF values of 370 and 720 were experimentally determined at equilibrium for rainbow trout exposed to water concentrations of 28 ng/L (ppb) and 670 ng/L (ppb), respectively, of 1,4-DCB for up to 119 days in laboratory aquaria (Oliver and Niimi 1983). BCF values measured in this study for 1,2-DCB were 270 (47 ng/L in water) and 560 (940 ng/L in water), while BCF values measured for 1,3-DCB were 420 (28 ng/L in water) and 740 (690 ng/L in water). A study of chlorobenzenes in sediments, water, and selected fish from the Great Lakes indicated that many chlorobenzenes are bioconcentrated by fish, but that DCBs are concentrated to a smaller extent than some of the more highly chlorinated chlorobenzene compounds such as pentachlorobenzene and hexachlorobenzene (Oliver and Niimi 1982a). For example, equilibrium/steady-

state BCF values measured in fish maintained in flowing water systems typically increased with increasing chlorination as shown in Table 6-4.

DCBs can enter soil-plant systems through many routes including atmospheric deposition, sewage sludge application to agricultural land, and through industrial activities (Wang and Jones 1994a). Wang and Jones (1994c) studied the uptake of several chlorobenzene compounds in carrots grown in spiked and sewage-amended soils. The transfer of chlorobenzenes from soils to plants and subsequent bioaccumulation is of interest because chlorobenzenes are ubiquitous in sewage sludge. Chlorobenzenes are also lipophilic and volatile compounds that can be taken up by plants by both root and foliage pathways. Carrots were grown for 100 days in control soil, chemically-spiked soil, and in low and high rate sludge-amended soils. DCB concentration in the soils did not remain constant throughout the growth period. BCF values are not traditional steady-state values since measurements were taken for only one time interval. The authors reported that concentrations of 1,4-DCB in soil before sowing and after the harvest were 5.9 and 2.6 ppb dry weight in the control, 16 and 11 ppb in the chemically-spiked soil, 10 and 7.4 ppb in the low rate sewage-amended soil, and 38 and 30 ppb in the high rate sewage-amended soils, respectively. Concentrations of 1,4-DCB in carrot foliage and the corresponding bioconcentration factors (BCFs) were 13 ppb (BCF=3.1) for the control, 17 ppb (BCF=1.3) for the spiked soil, 22 ppb (BCF=2.5) for the low rate sewage-amended soil, and 49 ppb (BCF=1.5) for the high rate sewage-amended soil. The concentrations of 1,2-DCB in soil before sowing and after the harvest were both below the detection limit (unspecified) in the control, 29 and 17 ppb in the chemically-spiked soil, 13 and 7.3 ppb in the low rate sewage-amended soil, and 60 and 45 ppb in the high rate sewage-amended soils, respectively. Concentrations of 1,2-DCB in carrot foliage and the corresponding BCFs were 6.7 ppb (BCF not given) for the control, 9.6 ppb (BCF=0.42) for the spiked soil, 12 ppb (BCF=1.2) for the low rate sewage-amended soil, and 26 ppb (BCF=0.49) for the high rate sewage-amended soil. The concentrations of 1,3-DCB in soil before sowing and after the harvest were both below the detection limit (unspecified) in the control, 4.2 and 2.9 ppb in the chemically-spiked soil, 2.3 and 0.98 ppb in the low rate sewage-amended soil, and 8.2 and 5.8 ppb in the high rate sewage-amended soils, respectively. Concentrations of 1,3-DCB in carrot foliage and the corresponding BCFs were 0.72 ppb (BCF not given) for the control, 0.83 ppb (BCF=0.24) for the spiked soil, 1.3 ppb (BCF=0.80) for the low rate sewage-amended soil, and 2.2 ppb (BCF=0.31) for the high rate sewage-amended soil. The application of the low-rate sewage sludge stimulated both the carrot foliage and root production to the greatest extent. The authors concluded that foliar uptake of all chlorobenzenes tested, including the DCBs, was an important bioaccumulation pathway.

Table 6-4. Comparison of Bioconcentration Factors (BCFs) for Various Chlorinated Benzenes in Fish

Compound	BCF (range)
Monochlorobenzene	12–450
1,2-Dichlorobenzene	89–560
1,3-Dichlorobenzene	66–740
1,4-Dichlorobenzene	15–720
1,2,3-Trichlorobenzene	700–2,600
1,2,4-Trichlorobenzene	182–3,200
1,3,5-Trichlorobenzene	760–4,100
1,2,3,4-Tetrachlorobenzene	3,800–12,000
1,2,3,5-Tetrachlorobenzene	1,800–3,900
1,2,4,5-Tetrachlorobenzene	4,000–13,000
Pentachlorobenzene	3,400–20,000
Hexachlorobenzene	12,000–44,437

Source: EPA 1985a

The concentrations (dry weight) of the DCBs in the carrot peel were typically equal to or slightly lower than the concentrations in the carrot core (Wang and Jones 1994a). This indicated that DCBs, when present in carrots, penetrate into the core. For carrot roots, the concentrations of 1,4-DCB in the core and peel were 9.4 μg/kg (ppb) (BCF=2.2) and 7.0 ppb (BCF=1.6) for the control, 5.9 ppb (BCF=0.44) and 7.3 ppb (BCF=0.54) for the chemically-spiked soil, 5.9 ppb (BCF=0.68) and 5.8 ppb (BCF=0.67) for the low-rate sewage application, and 9.6 ppb (BCF=0.28) and 4.3 ppb (BCF=0.13) for the high-rate sewage treatment, respectively. The concentrations of 1,2-DCB in the core and peel were 1.5 μg/kg (ppb) (BCF not given) and 1.4 ppb (BCF not given) for the control, 5.8 ppb (BCF=0.25) and 5.3 ppb (BCF=0.23) for the chemically-spiked soil, 0.0 ppb (BCF=0.0) and 0.84 ppb (BCF=0.085) for the low-rate sewage application, and 2.8 ppb (BCF=0.053) and 1.5 ppb (BCF=0.029) for the high-rate sewage treatment, respectively. 1,3-DCB was only detected in the core of the chemically-spiked soil at 1.0 ppb (BCF=0.29) and in the core of the high-rate sewage treatment at 1.8 ppb (BCF=0.26). 1,3-DCB concentrations in the root peels as well as the root core of the control were below the detection limit (unspecified). Overall, <1% of the DCBs and other chlorobenzenes in the soil were accumulated by the carrots, which is minor compared with the other loss pathway from the soil, principally volatilization.

Wang et al. (1996) found that a 1 ppm solution of 1,4-DCB was taken up by carrots (*Daucus carota*, 49%), soybeans (*Glycine max*, 50%), and red goosefoot (*Chenopodium rubrum*, 62%), but not by tomatoes *(Lycopersicon esculentum)*. Only the soybean cell cultures provided evidence of the existence of metabolites of this compound, probably conjugates of chlorophenol. The authors further observed that the uptake, metabolism, and toxicity of 1,4-DCB differed among the species tested.

Zhang et al. (2005) studied DCB uptake in vegetables grown in urban areas of China. DCB concentrations in spinach, Chinese cabbage, and celery were highest in roots, followed by leaves. Concentrations in radishes and carrots were highest in leaves, followed by stems. The authors reported that the accumulation of chlorinated benzenes in these vegetables was affected by the lipid contents of the vegetables, the volatilities of the chemicals, and the physiological characteristics of the vegetables.

Data on biomagnification of DCBs through aquatic or terrestrial food chains were not located.

6.3.2 Transformation and Degradation

6.3.2.1 Air

The main degradation pathway for DCBs in air is reaction with photochemically generated hydroxyl radicals (Cuppitt 1980; EPA 1985a). Reactions with ozone or other common atmospheric species are not expected to be significant (Cuppitt 1980; EPA 1985d). Therefore, the atmospheric lifetime of the DCBs may be predicted from an assumed hydroxyl radical concentration in air and the rate of reaction. The reported rate for reaction of hydroxyl radicals with DCBs is $3.2–7.2 \times 10^{-13}$ cm^3/mol-sec (Atkinson 1989; Howard 1989), and the estimated atmospheric half-life for DCBs is about 14–31 days (Howard 1989). Since this degradation process is relatively slow, DCBs may become widely dispersed, but are not likely to accumulate in the atmosphere. The degradation pathways for 1,4-DCB in the atmosphere are shown in Figure 6-4.

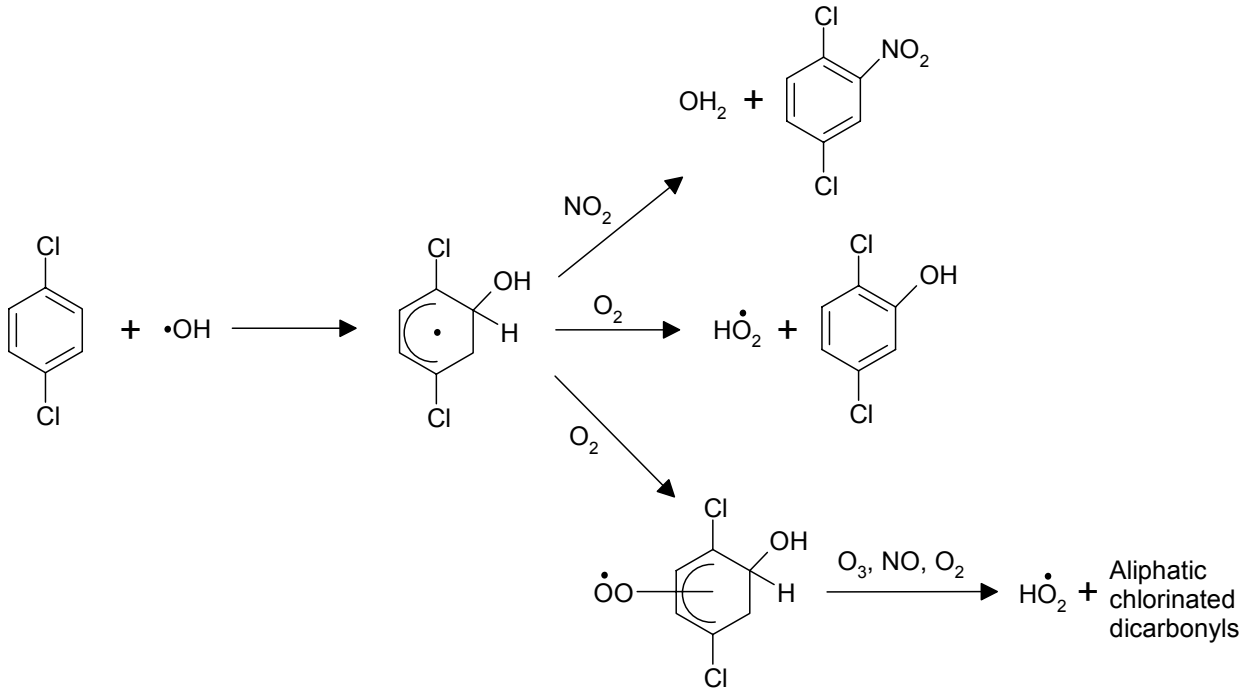
Reports of smog chamber studies of chlorobenzene degradation have indicated degradation after 5 hours of 21.5% of 1,2-DCB (EPA 1985a). Chloronitrobenzenes and chloronitrophenols were identified as degradation products. Irradiation of chlorobenzenes with natural sunlight was reported to produce polychlorinated biphenyls (PCBs). Whether this occurs under natural atmospheric conditions is unknown, but it would appear to be unlikely because of the normally low concentrations of chlorobenzenes in ambient air.

6.3.2.2 Water

Biodegradation may be an important transformation process for DCBs in water under aerobic, but not anaerobic, conditions (Bouwer and McCarty 1982, 1983, 1984; Schwartzenbach et al. 1983; Spain and Nishino 1987; Tabak et al. 1981). Although volatilization of 1,4-DCB may interfere with biodegradation studies, ^{14}C studies indicate that significant biodegradation of 1,4-DCB does occur (Spain and Nishino 1987). Longer acclimation periods are required when 1,4-DCB is the sole carbon source (Spain and Nishino 1987).

Several aerobic screening tests have been performed on the DCB isomers. 1,2- and 1,3-DCB, both at initial concentrations of 30 mg/L, reached 0% of their theoretical BOD in 4 weeks using an activated sludge inoculum at 100 mg/L and the Japanese MITI test (CITI 1992). During an OECD closed bottle test, removal of 1,4-DCB was 97.1%. However, volatilization was considered to be the major mechanism

Figure 6-4. The Decomposition of 1,4-Dichlorobenzene in Air



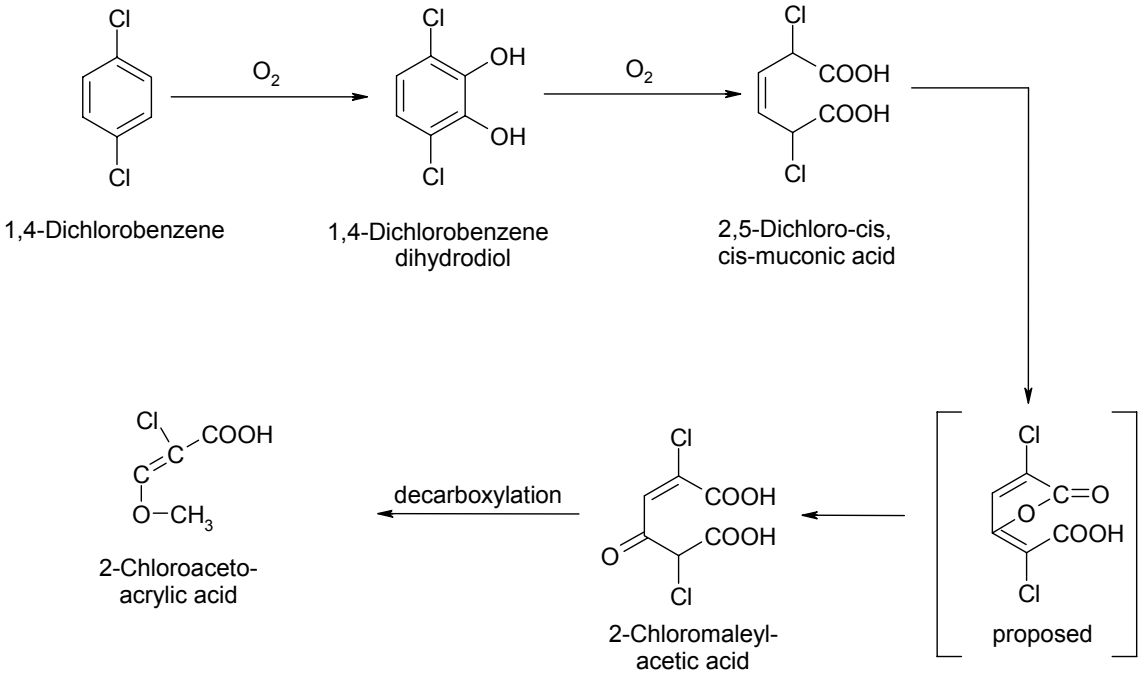
for removal. During a modified porous pot test operated under normal conditions at a lower aeration rate, temperatures of 8, 15, and 20 °C, and sludge retention times of 3 and 6 days, removal of 1,4-DCB was >95%. The author reported that the major mechanism for 1,4-DCB removal in this test was biodegradation. Using acetate as the primary carbon source under aerobic conditions and after an acclimation period of 10 days, rapid bacterial degradation of 96% of a 1,2-DCB sample, 28% of a 1,3-DCB sample, and 98% of a 1,4-DCB sample was reported (Bouwer and McCarty 1982). 1,4-DCB was completely mineralized to inorganic end products. Possible explanations for the lower 1,3-DCB biodegradation rate were biodegradation with slow utilization kinetics or sorption removal. The biodegradation rate of 1,2-DCB in a heterogeneous unconfined aquifer at Columbus Air Force Base in Columbus, Mississippi was measured to be 0.0059 day^{-1} (Stauffer et al. 1994). This corresponds to a half-life of 117 days. Biodegradation of 1,2-DCB in aquifer samples from Vejen and Grindsted, Denmark was slow, with >30% of the test compound remaining after 50 days. 1,4-DCB was not degraded in these samples after 50 days. 1,2-DCB (initial concentrations, 20 ppm) underwent 30–50% biodegradation in river water and 15–30% biodegradation in sea water after 3 days during an aerobic screening test (Kondo et al. 1988). 1,4-DCB (initial concentrations, 4 ppm) underwent 0% biodegradation in both the river water and sea water inocula after 3 days. *In-situ* biodegradation rate constants were measured for 1,2- and 1,4-DCB in an aerobic aquifer (Nielsen et al. 1996). Rate constants and lag phases were 0.02–0.06 day^{-1} (half-life, 12-35 days) and 0-20 days, respectively, for 1,2-DCB and 0.01–0.05 day^{-1} (half-life, 14–69 days) and 0–22 days, respectively, for 1,4-DCB. Half-lives reported for 1,4-DCB in seawater mesocosm experiments performed at various temperatures ranged from 10 to 18 days (Wakeham et al. 1983). The authors noted that volatilization was the dominant removal process. No degradation of DCBs was reported under denitrification or methanogenic conditions (Bouwer and McCarty 1983, 1984). Degradation pathways for 1,4-DCB in water are shown in Figure 6-5.

6.3.2.3 Sediment and Soil

Based on the Henry's law constants of 1,2- and 1,3-DCB and the tendency of 1,4-DCB to sublime, volatilization rather than transformation is the most likely fate process for DCBs from surface soil. Transformation of DCBs by biodegradation, photolysis, chemical hydrolysis, and oxidation appear to be relatively minor processes. Leaching of DCBs to groundwater from subsurface soils under certain conditions may occur (EPA 1985a).

Wang and Jones (1994a) studied the fate of chlorobenzenes including DCBs in chemically-spiked and sewage-amended soils to determine the rate of volatilization, biodegradation, photolysis, and other

Figure 6-5. The Decomposition of 1,4-Dichlorobenzene in Soil and Water



possible loss processes. These authors used sewage sludge collected from a sewage treatment facility serving a municipal (~60%) and industrial (~40%) catchment. The sewage sludge or chemically-spiked solutions containing chlorobenzenes were added to five experimental systems; (1) normal soil, (2) sterilized soil (with 1% [weight] of sodium azide), (3) sterilized soil shaded with aluminum foil, (4) sterilized soil, shaded and sealed with a Teflon-coated septum, and (5) a control (untreated soil). The mesocosms were incubated at 20–30 °C over a 259-day period. Loss of all chlorobenzenes including DCBs was best represented by a two-step first-order kinetics model. In the normal condition containing unsterilized soil exposed to sunlight and open to the air, during the first 35 days, 79.9% of the 1,2-DCB, 85.1% of the 1,3-DCB, and 70.5% of the 1,4-DCB were lost with half-life values of 13.2, 12.4, and 17.4 days, respectively. From day 35 to day 259, only 4.29% of 1,2-DCB, 3.93% of 1,3-DCB, and 11.3% of 1,4-DCB were lost with half-life values of 892, 579, and 294 days, respectively. For the chemically-spiked soil treatment, the first phase (days 0–17) loss was 75.6% for 1,2-DCB, 73.3% for 1,3-DCB, and 73.2% for 1,4-DCB with half-life values of 8.63, 8.42, and 8.57 days. The second phase (days 17–259) loss was 13.9% for 1,2-DCB, 25.4% for 1,3-DCB, and 11.2% for 1,4-DCB with half-lives of 191, 189, and 131 days, respectively. Although the DCB loss rates in the sewage-amended soil were slower than those in the chemically-spiked soil, the total percentage losses of DCBs after 259 days were comparable. Based on the results of losses of DCBs observed in the other microcosm systems, the authors concluded that transformation processes including biodegradation, photolysis, and other abiotic losses (chemical hydrolysis and oxidation) were minor processes compared to volatilization. The experimental results of Wang and Jones (1994a) showed that, during the first phase, volatilization rates were high and substantial portions of the DCBs were lost. The second phase was much slower and portions of the DCBs remained in the soil for a much longer period.

Neither 1,3- nor 1,4-DCB were biotransformed in an aerobic Rhine River sediment column (closed system) after 12 months (Bosma et al. 1990). 1,2-DCB was completely degraded after 4 months following a lag period of 60–100 days. DCBs (unspecified isomers) were degraded slowly in alkaline para-brown soil (100 g soil per 2 mg compound) with 6.3% of theoretical CO_2 evolution in a closed system after 10 weeks (Haider et al. 1974). Half-lives corresponding to the biodegradation of 1,2-, 1,3-, and 1,4-DCB in anaerobic estuarine sediment from the Tsurumi River, Japan were 36.9, 433.2, and 385.1 days, respectively (Masunaga et al. 1996). Between 25 and 90% of 1,2- and 1,4-DCB were removed from an aerobic soil column (closed system) after 300 days of continuous operation, while <25% of 1,3-DCB was removed (Van der Meer et al. 1992). These studies show that the rate of loss of DCBs in soils and sediments is much lower when volatilization is minimized. This supports the conclusion of Wang and Jones (1994a) that biodegradation is slow compared to volatilization.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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

Due to their use and volatile nature, DCBs are detected much more frequently and at higher concentrations in air than in other environmental compartments such as soil, water, or sediment.

6.4.1 Air

1,4-DCB has been detected in indoor air, ambient outdoor air, and in occupational settings. A summary of levels of 1,4-DCB detected in indoor air is shown in Table 6-5. An update of the 1980 national ambient VOCs database prepared for the EPA summarized concentrations of 1,4-DCB by site type (Shah and Heyerdahl 1988). The median indoor air concentration of 1,4-DCB detected at 2,121 sites was 0.283 ppb (mean 3.988 ppb), and the median concentration detected from personal air monitoring of 1,650 individuals was 0.416 ppb (Shah and Heyerdahl 1988); for reference, the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) (8-hour time-weighted average [TWA] for 1,4-DCB is 10 ppm (ACGIH 2005). The authors concluded that these values are a result of the use of 1,4-DCB in air fresheners and to control moths that could damage woolen clothing.

Because of its indoor uses, reports of indoor air monitoring show higher concentrations of 1,4-DCB than those observed in ambient outdoor air. This was also observed during the Total Exposure Assessment Methodology (TEAM) Study conducted by EPA between 1979 and 1985 in an effort to measure exposures to 20 VOCs in personal air, outdoor air, and drinking water. Data from the TEAM study were presented for the sum of 1,3- and 1,4-DCB (Wallace et al. 1986a). Because 1,4-DCB is produced and used in much greater volume than 1,3-DCB, the authors assumed that the concentrations found were almost all 1,4-DCB. The authors concluded that the major cause for the higher personal air

Table 6-5. Levels of 1,4-Dichlorobenzene in Indoor Air

Conditions	Concentration (ppm)				Reference
	Range	Mean	Median	Maximum	
Bathroom with one deodorizer block	7.80×10^{-2}–1.26×10^{-1}				Scuderi 1986
Bathroom with one deodorizer block in one urinal and one toilet	1.16×10^{-1}–2.20×10^{-1}				
Inside closet with moth flakes in closed garment bag	2.19×10^{-1}–5.45×10^{-1}				
Outside closet with moth flakes in closed garment bag	1.03×10^{-2}–7.10×10^{-2}				
Inside wardrobe air		0.197			Morita and Ohi 1975
Inside closet air		0.036			
Bedroom air		0.012			
2,121 Indoor sites		4×10^{-3}	2.83×10^{-4}		Shah and Heyerdahl 1988
1,650 Personal air monitors			4.16×10^{-4}		
1256 Dwellings		1.33×10^{-3}			Brown et al. 1994
Ventilated office air					Field et al. 1992
Prior to pollution event	4.43×10^{-3}–7.75×10^{-3}	5.14×10^{-3}	4.89×10^{-3}		
During pollution event	3.54×10^{-3}–7.29×10^{-3}	4.51×10^{-3}	4.48×10^{-3}		
32 Smoking homes		2.79×10^{-3}	1.51×10^{-4}	5.03×10^{-2}	Heavner et al. 1996
61 Nonsmoking homes		8.62×10^{-4}	9.65×10^{-5}	2.03×10^{-2}	
757 Homes		2.61×10^{-3}			Meek et al. 1994
12 Homes	1.66×10^{-4}–1.78×10^{-2}	2.50×10^{-3}			Chan et al. 1990
Over 100 homes (United States, Germany, Netherlands)		2.16×10^{-3} (3.99×10^{-3} in the United States)		2.66×10^{-1}	IARC 1999
Inside four test houses			3.65×10^{-4}–4×10^{-2}	1.2×10^{-3}–1.22×10^{-1}	Wallace et al. 1989
With solid deodorizer			5.64×10^{-2}		
With spray deodorizer			6.14×10^{-3}		
With liquid deodorizer			4.15×10^{-3}		
With no deodorizer			4.32×10^{-3}		
26 Normal houses		1.08×10^{-4}	1.33×10^{-5}	1.5×10^{-3}	Kostiainen 1995

Table 6-5. Levels of 1,4-Dichlorobenzene in Indoor Air

Conditions	Concentration (ppm)				Reference
	Range	Mean	Median	Maximum	
Nationwide study of Canadian homes					Fellin and Otson 1994
Winter		5.93×10^{-3}			
Spring		2.5×10^{-3}			
Summer		1.75×10^{-3}			
Fall		2.5×10^{-3}			
0 °C		3.92×10^{-3}			
0–15 °C		3.66×10^{-3}			
15 °C		2.0×10^{-3}			

concentrations was the use of 1,4-DCB sources such as moth crystals and room deodorizers in the home (Wallace et al. 1986b).

Wallace et al. (1989) studied the influence of personal activities on exposure to VOCs. These authors reported that the median 1,4-DCB concentration in ambient outdoor air sampled 3 times/day over a 3-day monitoring period at each of three test houses was <1 μg/m^3 (0.17 ppb) and the maximum concentration was 17 μg/m^3 (2.8 ppb). The median indoor 1,4-DCB air concentrations sampled individually at each of four study houses ranged from 2.2 to 240 μg/m^3 (0.37–40 ppb), while the maximum concentrations ranged from 7.2 to 740 μg/m^3 (1.2–123.3 ppb). The mean personal air concentration for seven individuals living in the study houses was 81 μg/m^3 (13.5 ppb) (range 4.0–240 μg/m^3 [0.7–40 ppb]), while the outdoor mean 1,4-DCB personal air concentration was 1 μg/m^3 (0.17 ppb). The personal air to outdoor air ratio of 81 was 4 times higher than the ratios calculated for the other VOCs tested. Two individuals living in the same house both had mean personal air concentrations of 240 μg/m^3 (40 ppb); the median levels of 1,4-DCB in their breath were 40 and 47 μg/m^3 (6.7 and 7.8 ppb), which was higher than the median breath level of 1.5 μg/m^3 (0.3 ppb) in an individual receiving a personal exposure of 5.7 μg/m^3 (1.5 ppb). Wallace et al. (1989) further studied the activities associated with increased personal exposure to, or increased indoor air concentrations of, 1,4-DCB. The activities that increased both personal exposure and indoor air concentrations of 1,4-DCB were the use of solid toilet deodorizers, followed by spray deodorizers and liquid deodorizers, compared to the use of no deodorizers at all. The median personal exposure concentrations to 1,4-DCB were 330 μg/m^3 (55 ppb) (maximum, 500 μg/m^3 [83.3 ppb]), 33 μg/m^3 (5.5 ppb) (maximum, 84 μg/m^3 [14 ppb]), 12 μg/m^3 (2 ppb) (maximum, 28 μg/m^3 [4.7 ppb]), and 2.4 μg/m^3 (0.4 ppb) (maximum, 6.6 μg/m^3 [1.1 ppb]) for solid, spray, liquid, and no deodorizer use, respectively. Median indoor air concentrations were 340 μg/m^3 (56.7 ppb) (maximum, 630 μg/m^3 [105 ppb]), 37 μg/m^3 (6.2 ppb) (maximum, 59 μg/m^3 [9.8 ppb]), 25 μg/m^3 (4.2 ppb) (maximum, 30 μg/m^3 [5 ppb]), and 2.6 μg/m^3 (0.43 ppb) (maximum, 5.2 μg/m^3 [0.87 ppb]) for solid, spray, liquid, and no deodorizer use, respectively.

More recently, Kostianen (1995) identified >200 VOCs in the indoor air of 26 normal houses. 1,4-DCB was detected in 100% of the houses studied. 1,4-DCB was detected at a mean concentration of 0.65 μg/m^3 (0.1 ppb) (median 0.08 μg/m^3 [0.013 ppb], minimum 0 μg/m^3 [0 ppb], and maximum 8.94 μg/m^3 [1.5 ppb]) in the houses studied. Forty-eight compounds (including 1,4-DCB) were selected for further quantitative analysis in 50 normal houses and 38 “sick houses,” which had poor quality indoor air that was linked to odors and to a number of physiological follow-up study of normal and “sick houses,” the median concentration of 1,4-DCB (0.88 μg/m^3 [0.15 ppb]) in the normal houses was

exceeded by 5–10% in 6% of the normal houses and by 10–50% in 18% of the normal houses, while in the "sick houses," the median concentration was exceeded by 5–10% in 7.9% of the "sick houses", by 10–50% in 2.6% of the sick houses, and by 50–200% in 5.3% of the "sick houses." The median concentrations of 1,4-DCB reported in the 38 "sick houses" ranged from 0.00 to 5.36 μg/m^3 (0–0.89 ppb).

During a study of exposure of volatile organic compounds in the air of three photocopy centers, 1,4-DCB was detected in the breathing zone of photocopier operators at concentrations ranging from 0.1 to 3.7 ppb (Stefaniak et al. 2000). 1,4-DCB was not listed with the compounds detected in building background samples.

A nationwide study of indoor air concentrations of 26 VOC compounds was conducted in Canada in 1991 (Fellin and Otson 1994). The authors reported that mean 1,4-DCB concentrations were 35.75 μg/m^3 (5.96 ppb) (winter), 15 μg/m^3 (2.5 ppb) (spring), 10.54 μg/m^3 (1.76 ppb) (summer), and 15 μg/m^3 (2.5 ppb) (fall), and that the concentrations declined with an increase in ambient air temperature. At ≤0, 0–15, and ≥15 °C, the 1,4-DCB mean concentrations were 23.64, 22.02, and 11.83 μg/m^3 (3.94, 3.67, and 1.97 ppb), respectively. Analysis revealed that 1,4-DCB concentrations were associated with use of household products and moth repellant crystals. These authors concluded that indoor sources of 1,4-DCB (household products and moth repellant crystal) are likely to have a more significant influence on indoor air concentrations than climatic variables. Summer conditions and outdoor temperatures >15.1 °C gave the lowest indoor air concentrations of 1,4-DCB. Moth repellant crystals are also deployed in a manner that gives reasonably constant emissions over several weeks. This compound produced a trend consistent with expected ventilation results. The highest average concentrations were observed during the winter or when temperatures were <0 °C, when ventilation is expected to be lowest. Intermediate values were measured during the fall and spring, while the lowest values were measured during the summer, when ventilation of homes is expected to be highest. Zhu et al. (2005) detected 1,2- and 1,4-DCB in the indoor air samples from 5 and 81% of 75 randomly selected dwellings in Ottawa, Canada, respectively. Arithmetic mean concentrations in these air samples were 0.77 μg/m^3 for 1,4-DCB and 0.01 μg/m^3 for 1,2-DCB.

Kinney et al. (2002) measured home outdoor, home indoor, and personal air concentrations of 1,4-DCB for selected students that attend school in the West Central Harlem section of New York City as part of the Toxic Exposure Assessment (TEACH) study. Mean winter concentrations of 1,4-DCB were 5.03 μg/m^3 in 36 home outdoor samples, 54.9 μg/m^3 in 36 home indoor samples, and 43.4 μg/m^3 in 36 personal air samples. Mean summer concentrations of 1,4-DCB were 5.03 μg/m^3 in 29 home outdoor

samples, 54.9 μg/m^3 in 36 home indoor samples, and 43.4 μg/m^3 in 40 personal air samples. Similar results were obtained from TEACH study measurements in Los Angeles, California (Sax et al. 2004). Mean outdoor 1,4-DCB concentrations were 2.0 μg/m^3 in 35 samples collected during the winter and 3.5 μg/m^3 in 32 samples collected during the fall. Mean indoor 1,4-DCB concentrations were 40 μg/m^3 in 40 samples collected during the winter and 52 μg/m^3 in 32 samples during the fall. Personal air concentrations measured in Los Angeles were not reported in this study. Shendell et al. (2004) measured 1,4-DCB concentrations ranging from not detected to 3.36 μg/m^3 in the air of 13 portable modular classroom structures and from not detected to 10 μg/m^3 in the air of 7 main building classrooms (Shendell et al. 2004). Mean and median 1,4-DCB concentrations in air from 3 urban communities in Minnesota (Battle Creek, East St. Paul, and Phillips) were measured to be 0.1 and 0.1 μg/m^3, respectively, in 132 outdoor air samples, 1.2 and 0.2 μg/m^3, respectively, in 292 indoor air samples, and 3.2 and 0.4 μg/m^3, respectively, in 288 personal air samples (Sexton et al. 2004).

1,4-DCB has been detected in ambient air samples in several monitoring studies, as shown in Table 6-6. Kelly et al. (1994) reported that the median concentration of 1,4-DCB was below detection limits based on 1,447 samples collected from 57 different locations. MacLeod and Mackay (1999) reported a 1,4-DCB background concentration of 3.36×10^{-5} ppm for the Southern Ontario, Canada region. The mean and median concentrations of 1,4-DCB in air from 25 sites across the state of Minnesota were 3.36×10^{-5} and 2.55×10^{-5} ppm, respectively (Pratt et al. 2000). Concentrations were not quantifiable in rural air (Shah and Heyerdahl 1988), but increasingly higher concentrations were detected in suburban and urban air. Air samples from Mexicali, Mexico, a residential industrial area, contained 1,4-DCB with concentrations ranging from 6.0×10^{-5} to 2.22×10^{-2} ppm (mean=1.75×10^{-3} ppm), while air samples from Rosarito, Mexico, a beach resort town, contained 1,4-DCB with concentrations ranging from 2.0×10^{-5} to 1.8×10^{-4} ppm (mean=8.0×10^{-5} ppm). Hartwell et al. (1992) reported that ambient outdoor concentrations of 1,4-DCB are considerably higher in the winter compared to the summer. The authors concluded that this effect may be due to reduced levels of sunlight in the winter, which would hinder atmospheric removal by photooxidation. Mean concentrations of 1,4-DCB in air, and in the vicinity of hazardous waste sites and sanitary landfill sites, generally average $<4.2 \times 10^{-3}$ ppm, but indoor air concentrations of 1,4-DCB may be 1–3 orders of magnitude higher where 1,4-DCB is used as a space deodorizer or moth repellent (IARC 1982; Scuderi 1986; Wallace et al. 1986a, 1986b) (see Table 6-5).

Concentrations of 1,4-DCB in workplace air were, not unexpectedly, the highest concentrations measured (IARC 1982), as shown in Table 6-7; concentrations ranged from 33–52 mg/m^3 (5.4–8.7 ppm) detected in

Table 6-6. Levels of 1,4-Dichlorobenzene in Outdoor Air

Location	Concentration (ppm)				Reference
	Mean	Median	Maximum	Range	
Rural		0.00[a]			Shah and Heyerdahl 1988
Semi-rural (NJ)	$2.0x10^{-5}$–$2.1x10^{-4}$[b]		$1.7x10^{-4}$–$4.6x10^{-3}$[c]		Bozzelli and Kebbekeus 1979
Suburban		$4.8x10^{-5}$			Shah and Heyerdahl 1988
Suburban	$1.5x10^{-4}$			$5.0x10^{-5}$–$5.0x10^{-4}$	Delfino et al. 2003
Suburban			$2.8x10^{-3}$	<$1.66x10^{-4}$–$2.8x10^{-3}$	Wallace et al. 1989
Suburban	$4.06x10^{-4}$				Bevan et al. 1991
Urban		$5x10^{-5}$			Shah and Heyerdahl 1988
Urban (NJ)					Harkov et al. 1984
Summer	$4x10^{-5}$–$7x10^{-5}$[d]				
Winter	$2x10^{-5}$[d]				
Urban (NJ)	$6x10^{-5}$[d] $5x10^{-5}$–$6.6x10^{-4}$[b]		$4.3x10^{-4}$–$2x10^{-2}$[c]		Bozzelli and Kebbekeus 1979
Urban (DC)	$1.5x10^{-4}$		$1.57x10^{-3}$		Hendler and Crow 1992
Urban	$6.96x10^{-5}$			0.0–$2.44x10^{-4}$	Fraser et al. 1998
Urban	$1.42x10^{-4}$			<$2.0x10^{-4}$–$1.3x10^{-3}$	Loscutoff and Poore 1993
Urban	0.00–$7.00x10^{-5}$		$2.20x10^{-4}$		Zielinska et al. 1998
Urban	$2.0x10^{-2}$ $2.9x10^{-1}$		$2.9x10^{-2}$ $1.0x10^{1}$		Grosjean 1991
Urban	$4.18x10^{-4}$				Bevan et al. 1991
Hazardous waste sites (seven sites)	$3x10^{-5}$–$5.4x10^{-4}$[b]		$4.2x10^{-3}$		Harkov et al. 1984
Hazardous waste sites and sanitary landfill sites	$4x10^{-5}$–$5.1x10^{-4}$[b] $2x10^{-5}$–$2.2x10^{-4}$[e]		$3.8x10^{-4}$–$4.2x10^{-3}$[c]		LaRegina et al. 1986
Waste dump				$1.24x10^{-5}$–$6.41x10^{-5}$	Nerin et al. 1996

[a]Level not quantifiable
[b]Range in arithmetic mean concentrations
[c]Range in maximum concentrations detected
[d]Geometric mean
[e]Range in geometric mean concentrations

Table 6-7. Levels of 1,4-Dichlorobenzene Detected in Workplace Air

Occupation	Concentration (ppm)	
	Maximum	Range
Monochlorobenzene manufacturing plant	8.7	5.4–8.7
Abrasive-wheel plant	11.5	8–11.5
Mothball manufacturing plant	25	9–25
Chlorobenzene manufacturing plant	34	24–34
1,4-Dichlorobenzene manufacturing plant	548	12–548
Monochlorobenzene and dichlorobenzene manufacturing plant	724	–

Source: IARC 1982

air sampled at a monochlorobenzene manufacturing facility to 4,350 mg/m^3 (724 ppm) detected in air sampled at a plant manufacturing monochlorobenzene and DCB.

1,2- and 1,3-DCB have also been detected in air samples from various locations, though at much lower concentrations than 1,4-DCB. Because these isomers are not used in household products to the extent that 1,4-DCB is, they are not prevalent in indoor air. For example, mean indoor air concentrations in a ventilated office in London were approximately 3.5x10^{-3} ppm for 1,4-DCB compared to 1.4x10^{-4} ppm for 1,2-DCB (Field et al. 1992). Mean indoor air concentrations of 1,2-DCB from residences in some California communities were 1.39x10^{-5} ppm during the winter and 3.48x10^{-6} ppm during the summer (Pellizzari et al. 1986). 1,3-DCB was detected in the air from a university art building where there is heavy use of printmaking solvents. Mean concentrations of 1,3-DCB were 0.4 μg/m^3 (median=0.8 μg/m^3) on the studio floor and 0.8 μg/m^3 (median below 0.5–1.5 ppb) on a non-use floor (Ryan et al. 2002). Some studies have reported 1,3-DCB air sample concentrations in combination with 1,4-DCB concentrations. However, based the production volumes of these isomers, it is expected that these concentrations represent 1,4-DCB almost entirely. The concentrations of 1,2- and 1,3-DCB measured in ambient outdoor air are shown in Tables 6-8 and 6-9, respectively. Based on the data in these tables, ambient outdoor air concentrations generally range from 0.01 to 0.1 ppb for 1,2-DCB, and from 0.001 to 0.1 ppb for 1,3-DCB. Concentrations of 1,2- and 1,3-DCB in workplace air were not located.

6.4.2 Water

DCBs have generally been detected at low concentrations in finished drinking water, surface water, and groundwater in the United States. Finished drinking water samples from 20 of the 113 cities monitored in the National Organics Monitoring Survey (NOMS) had levels of 1,4-DCB ranging from 0.01 to 1.54 ppb, with a median value of 0.03 ppb (Dressman et al. 1977), and the compound was detected in about 13% of finished drinking water supplies using surface water sources (Coniglio et al. 1980). 1,2-, 1,3- and 1,4-DCB were reported in drinking water samples from three cities on Lake Ontario at concentrations ranging from not detectable (ND) to 2 ppt, from ND to 7 ppt, and from 8 to 20 ppt, respectively (Oliver and Nicol 1982a). DCB isomers were detected in 0–3% of drinking water samples from selected locations in New Jersey, North Carolina, and North Dakota locations (Wallace et al. 1986a). Concentrations of 1,3- and 1,4-DCB were generally <1 μg/L in treated and raw water samples taken from 30 Canadian potable water treatment facilities that serve about 5.5 million consumers (Otson et al. 1982).

Table 6-8. Levels of 1,2-Dichlorobenzene in Outdoor Air

Location	Concentration (ppm)				Reference
	Mean	Median	Maximum	Range	
Semi-rural (New Jersey)	$2x10^{-5}$–$2.4x10^{-4}$[a]		$2.1x10^{-4}$–$3.9x10^{-3}$[b]		Bozzelli and Kebbekeus 1979
Beach resort town	$3.0x10^{-5}$			$1.0x10^{-5}$–$8.0x10^{-5}$	Zielinska et al. 2001
Background (Southern Ontario)	$1.28x10^{-6}$				MacLeod and Mackay 1999
25 Sites across Minnesota	$1.62x10^{-5}$	$1.28x10^{-5}$	$2.44x10^{-5}$		Pratt et al. 2000
Urban (New Jersey)					Harkov et al. 1984
Summer	$1x10^{-5}$–$3x10^{-5}$[c]				
Winter	$3x10^{-5}$–$6x10^{-5}$[c]				
Urban (New Jersey)	$4.8x10^{-5}$[c] $2x10^{-5}$–$1.0x10^{-3}$[a]		$5.2x10^{-4}$–$1x10^{-2}$[b]		Bozzelli and Kebbekeus 1979
Urban (seven U.S. cities)	$4.0x10^{-6}$–$2.60x10^{-5}$			$1.0x10^{-6}$–$2.36x10^{-4}$	Singh et al. 1981a, 1981b
Urban	$2.0x10^{-5}$			$1.0x10^{-5}$–$6.0x10^{-5}$	Zielinska et al. 2001
Urban	$8.6x10^{-5}$			$<1.0x10^{-4}$–$6.0x10^{-4}$	Loscutoff and Poore 1993
Urban	0.0[d]–$8.80x10^{-4}$		$1.02x10^{-3}$		Zielinska et al. 1998
Urban	$1.0x10^{-3}$–$1.3x10^{-1}$ $5.6x10^{-2}$		$1.7x10^{-3}$–$3.1x10^{-1}$[d] $6.6x10^{-1}$		Grosjean 1991
Hazardous waste sites and sanitary landfill sites	$6x10^{-5}$–$7.7x10^{-4}$[a] $2x10^{-5}$–$2.3x10^{-4}$[e]		$6.9x10^{-4}$–$8.4x10^{-3}$[b]		LaRegina et al. 1986
Waste dump				$1.58x10^{-5}$–$9.13x10^{-5}$	Nerin et al. 1996

[a]Range in arithmetic mean concentrations
[b]Range in maximum concentrations detected
[c]Geometric mean
[d]Level not quantifiable
[e]Range in geometric mean concentrations

Table 6-9. Levels of 1,3-Dichlorobenzene in Outdoor Air

Location	Concentration (ppm)				Reference
	Mean	Median	Maximum	Range	
Beach resort town			0.00[a]		Zielinska et al. 2001
Background (Southern Ontario)	1.39×10^{-6}				MacLeod and Mackay 1999
25 Sites across Minnesota	2.55×10^{-5}	1.28×10^{-5}	9.87×10^{-4}		Pratt et al. 2000
Urban (seven U.S. cities)	4.0×10^{-6}–8.7×10^{-6}			1.0×10^{-6}–4.7×10^{-5}	Singh et al. 1981a, 1981b
Urban			0.00[a]		Zielinska et al. 2001
Urban	1.01×10^{-4}			$<2.0 \times 10^{-4}$–3.0×10^{-4}	Loscutoff and Poore 1993
Urban	0.0[a]–8.80×10^{-4}		1.02×10^{-3}		Zielinska et al. 1998
Urban	4.0×10^{-3}–7.7×10^{-2} 8.3×10^{-2}		9×10^{-3}–1.5×10^{-1}[b] 2.2		Grosjean 1991
Waste dump				1.43×10^{-6}–6.70×10^{-6}	Nerin et al. 1996

[a]Level not quantifiable
[b]Range in maximum concentrations detected

During a national groundwater supply survey, 1,4-DCB was detected in 2 out of 280 (0.7%) random sample sites serving <10,000 persons and in 3 out of 186 (1.6%) random sample sites serving >10,000 persons above a quantitation limit of 0.5 μg/L (Westrick et al. 1984). The mean positive concentration and maximum value were 0.60 and 0.68 μg/L, respectively, for the sites serving <10,000 persons and 0.66 and 1.3 μg/L, respectively, for the sites serving >10,000 persons. 1,2- and 1,3-DCB were not detected above the quantitation limit (0.5 μg/L) in any of the random samples. 1,4-DCB was detected above 0.5 μg/L in 4 out of 321 (1.2%) nonrandom sample sites serving <10,000 persons with a median positive concentration of 0.74 μg/L and a maximum value of 0.90 μg/L. This compound was not detected above 0.5 μg/L in 158 nonrandom sample sites serving >10,000 persons. 1,2-DCB was detected above 0.5 μg/L in 1 out of 321 (0.3%) nonrandom sample sites serving <10,000 persons at a concentration of 2.2 μg/L and in 1 out of 158 (0.6%) nonrandom sample sites serving >10,000 persons at a concentration of 2.7 μg/L. 1,3-DCB was not detected above 0.5 μg/L in any of the nonrandom samples. Stackelberg et al. (2001) detected 1,2-, 1,3-, and 1,4-DCB in approximately 8, 4, and 8%, respectively, of samples collected from 30 public supply wells in southern New Jersey. Concentrations or limits of detection were not reported. 1,4-DCB had two detections at concentrations that were both below a laboratory reporting limit of 0.05 μg/L in samples from 178 active public supply wells in the Los Angeles physiographic basin (Shelton et al. 2000). 1,2- and 1,3-DCB were analyzed for, but were not detected in any of the samples from these wells. The laboratory reporting limits used for 1,2-DCB were 0.031 and 0.048 μg/L. The laboratory reporting limits used for 1,3-DCB were 0.03 and 0.054 μg/L.

1,2-DCB was detected in 0.6% of 1,077 surface water samples recorded in the STORET database at a median concentration of <10 ppb (Staples et al. 1985). 1,3-DCB was detected in 0.3% of 986 surface water samples recorded in the STORET database at a median concentration of <10 ppb. 1,4-DCB was detected in 3% of 8,576 surface water samples recorded in the STORET database at a median concentration of <0.1 ppb. 1,4-DCB was detected in 100% of 91 surface water samples from the Great Lakes at mean concentrations ranging from 0.28 ppt in Lake Huron to 1.5 ppt in Lake Ontario (IJC 1989). Oliver and Nicol (1982a) also reported concentrations of DCBs in water samples collected from the Great Lakes region. Mean 1,2-DCB concentrations were 5 ppt (range, 2–7 ppt) in samples from Lake Ontario and 6 ppt (range, ND–31 ppt) in samples from the Grand River. 1,2-DCB was not detected in samples from Lake Huron. Mean 1,3-DCB concentrations were 1 ppt (range, ND–4 ppt) in samples from the Grand River. 1,3-DCB was not detected in samples from Lake Ontario or Lake Huron. Mean 1,4-DCB concentrations were 45 ppt (range, 33–64 ppt) in samples from Lake Ontario, 4 ppt (range, 3–6 ppt) in samples from Lake Huron, and 10 ppt (range, ND–42 ppt) in samples from the Grand River. During a

study of contaminants in 139 streams located in 30 states, 1,4-DCB was detected in 25.9% of samples in which it was searched for, with a median concentration of 0.09 μg/L and a maximum concentration of 4.3 μg/L (Kolpin et al. 2002).

Concentrations of 1,2-, 1,3- and 1,4-DCB from the Niagara River sampled in 1980 ranged from ND to 56 ppt, from ND to 56 ppt, and from 1 to 94 ppt. The highest concentration of 1,2- and 1,4-DCB occurred just below a chemical manufacturing plant's effluent discharge, while the highest concentration of 1,3-DCB occurred just below a waste disposal dump (Oliver and Nicol 1982a). 1,2-, 1,3-, and 1,4-DCB were also reported in waste water effluent samples collected from four plants on the Great Lakes at mean concentrations of 13 ppt (range, 6–22 ppt), 14 ppt (range, 7–13 ppt), and 660 ppt (range, 484–920 ppt) (Oliver and Nicol 1982a). In a New Jersey survey, 1,2-, 1,3- and 1,4-DCB were detected in 3, 4, and 6%, respectively, of 463 surface water samples (Page 1981). Maximum concentrations were 8.2 ppb for 1,2-DCB, 242 ppb for 1,3-DCB, and 31 ppb for 1,4-DCB. DCBs have been reported in surface waters in the vicinity of hazardous waste sites at unspecified concentrations (Elder et al. 1981) and at a concentrations of 9 ppt (1,2-DCB), 18 ppt (1,3-DCB), and 52 ppt (1,4-DCB) (Oliver and Nicol 1982a).

DCBs were monitored in wetland-treated leachate water at a municipal solid waste landfill site in central Florida from 1989 to 1990 and from 1992 to 1993 (Chen and Zoltek 1995). During the first sampling period, surface water samples contained 1,2-DCB at concentrations ranging from 0.02 to 0.10 ppb, 1,3-DCB at concentrations ranging from 0.02 to 0.10 ppb, and 1,4-DCB at concentrations ranging from 0.04 to 0.13 ppb. Groundwater samples contained 1,2-DCB at concentrations ranging from 0.09 to 1.56 ppb, 1,3-DCB at concentrations ranging from 0.08–8.95 ppb, and 1,4-DCB at concentrations ranging from 0.08 to 10.71 ppb. During the second sampling period (1992–1993), the three DCB isomers were not detected in surface water samples. 1,2- and 1,4-DCB were each detected in two groundwater samples at concentrations ranging from 0.75 to 0.84 ppb and from 0.45 to 3.74 ppb, respectively. 1,3-DCB was not detected in groundwater samples collected during the second sampling period. No detection limits were given. DCB (isomers unspecified) was detected in a study of three landfills in central Florida (Hallbourg et al. 1992). These authors reported DCB concentration ranges in groundwater of 0.37–21.2, 6–46.4, and <1–7.4 μg/L (ppb) at three different landfill sites. Plumb (1991) reported that 1,2-, 1,3-, and 1,4-DCB were detected in groundwater collected at 36, 16, and 34 of 479 hazardous waste sites, respectively. This author reported that 1,2-DCB was detected in 240 samples collected from 36 sites in 9 of the 10 EPA regions, 1,3-DCB was detected in 82 samples collected from 16 sites in 8 of the 10 EPA regions, and 1,4-DCB was detected in 191 samples collected from 34 sites in 9 of the 10 EPA regions.

Untreated, ambient groundwater samples from 406 urban wells and 2,542 rural wells from across the conterminous United States were collected between 1985 and 1995 as a part of the National Water-Quality Assessment Program (NAWQA) of the U.S. Geological Survey (Squillace et al. 1999). 1,2-DCB was detected in 1.4% of the urban well samples with a median concentration of approximately 0.2 μg/L (range 0.2–100 μg/L). This compound was detected in 0.2% of the rural well samples with a median concentration of approximately 1 μg/L (range 0.3-5 μg/L). 1,4-DCB was detected in 1.8% of the urban well samples with a median concentration of approximately 1 μg/L (range 0.3–50 μg/L). It was detected in 0.2% of the rural well samples with a median concentration of approximately 1.5 μg/L (range 0.6–8 μg/L). 1,3-DCB was not included in this study. Similar results were reported by Moran et al. (2004) in a summary of 1985-1999 NAWQA monitoring data involving chemical concentrations measured in 1,926 rural private wells. 1,2- and 1,3-DCB were not detected at all, while 1,4-DCB was detected in only 1 out of 1,925 samples at a concentration of 1.2 μg/L. 1,2-, 1,3-, and 1,4-DCB were detected in approximately 25, 15, and 10%, respectively, of samples collected from 95 monitoring wells in southern New Jersey, respectively (Stackelberg et al. 2001). Concentrations or limits of detection were not reported. In a separate New Jersey survey, 1,2-, 1,3-, and 1,4-DCB were detected in 3, 2, and 3 of 685 groundwater samples (Page 1981). Maximum concentrations were 6,800 ppb for 1,2-DCB, 237 ppb for 1,3-DCB, and 995 ppb for 1,4-DCB. 1,4-DCB had a frequency of detection of approximately 10% and a maximum concentration of 1.7 μg/L in groundwater samples from 29 alluvial wells beneath the Denver, Colorado area (Bruce and McMahon 1996). The authors also analyzed for 1,3-DCB, although it was not detected above the minimum detection level (0.2 μg/L) in any of the samples. 1,3-DCB was detected in two groundwater samples from five developing urban sites in the Upper Colorado River Basin with an estimated maximum concentration of 0.01 μg/L (Apodaca et al. 2002).

6.4.3 Sediment and Soil

Little information on soil concentrations of DCBs was located for the United States. One study conducted in England, however, reported DCB concentrations in agricultural soils increased during the 1960s, corresponding to a period of increased production of chlorobenzene compounds (Wang et al. 1995). The mean 1,4-DCB soil concentration reported for agricultural land was 2.17 ppb in 1942, 0.75 ppb in 1951, 1.73 ppb in 1960, 9.82 ppb in 1967, 3.9 ppb in 1972, 3.06 ppb in 1980, 1.4 ppb in 1984, and 0.4 ppb in 1991. The mean 1,3-DCB soil concentration was 0.20 ppb in 1960, 0.31 ppb in 1967, 0.36 ppb in 1972, and 0.30 ppb in 1980. 1,3-DCB soil concentrations were below the detection limit (0.2 ppb) in 1942, 1951, 1984, and 1991. 1,2-DCB soil concentrations were below the detection limit

(0.2 ppb) during all 8 sampling years. It should be noted that 1,4-DCB has been reported to occur in soils as a result of lindane degradation (EPA 1980a; IARC 1982), so the detection of 1,4-DCB may not be indicative of 1,4-DCB disposal *per se*.

1,2-DCB was detected in 0.9% of 352 sediment samples, 1,3-DCB was detected in 0.3% of 357 sediment samples, and 1,4-DCB was detected in 2% of 357 sediment samples recorded on the STORET database (Staples et al. 1985). DCBs have been detected in sediments near hazardous waste sites (Elder et al. 1981; Hauser and Bromberg 1982). During a study of semivolatile organic compounds in streambed sediment, 1,2-DCB was detected in 0.6% of samples collected at 516 sites from 20 major river basins in the United States during 1992–1995 with a maximum concentration of 86 μg/kg (95th percentile, <50 μg/kg) (Lopes and Furlong 2001). 1,4-DCB was detected in 1.2% of samples collected at 518 sites with a maximum concentration of 140 μg/kg (95th percentile, <50 μg/kg). 1,3-DCB was not detected in samples collected from 516 sites. The concentrations of 1,2- and 1,4-DCB were both <100 μg/kg in streambed sediment samples from 9 out of 14 river sites in the New England Coastal Basin (USGS 2002). Both of these compounds were at concentrations below the minimum reporting level (50 μg/kg) in samples from the remaining five river sites. Redmond et al. (1996) detected 1,2-, 1,3-, and 1,4-DCB at concentrations up to 4.4, 7.2, and 3.6 mg/kg, respectively, in the sediment of the Calcasieu River estuary, Louisiana.

Oliver and Nicol (1982a) reported DCB concentrations in surficial sediments from 13 sites in Lake Superior, 42 sites in Lake Huron, 5 sites in Lake Erie, and 11 sites in Lake Ontario. Mean 1,2-DCB concentrations detected were 1 ppb (range, ND–1 ppb), 8 ppb (range, ND–56 ppb), 2 ppb (range, 1–4 ppb), and 11 ppb (range, 4–27 ppb) for Lakes Superior, Huron, Erie, and Ontario, respectively. Mean 1,3-DCB concentrations detected were 2 ppb (range, ND–7 ppb), 2 ppb (range, ND–14 ppb), 4 ppb (range, 1–9 ppb), and 74 ppb (range, 15–250 ppb) for Lakes Superior, Huron, Erie, and Ontario, respectively. Mean 1,4-DCB concentrations detected were 5 ppb (range, ND–9 ppb), 16 ppb (range, 2–100 ppb), 9 ppb (range, 3–20 ppb), and 94 ppb (range, 22–210 ppb) for Lakes Superior, Huron, Erie, and Ontario, respectively. These authors also reported detecting DCB concentrations in deep sediment layers in Lake Ontario from core samples from the Niagara Basin. Concentrations of 1,2-DCB in various depths of the sediment cores were as follows: 14 ppb (0–1 cm), 15 ppb (1–2 cm), 19 ppb (2–3 cm), 16 ppb (3–4 cm), 26 ppb (4–5 cm), 13 ppb (5-6 cm), and 2 ppb (6–7 cm). Concentrations of 1,3-DCB in various depths of the sediment cores were as follows: 240 ppb (0–1 cm), 330 ppb (1–2 cm), 190 ppb (2–3 cm), 48 ppb (3–4 cm), 38 ppb (4–5 cm), 17 ppb (5–6 cm), and 4 ppb (6–7 cm). Concentrations of 1,4-DCB in various depths of the sediment cores were as follows: 110 ppb (0–1 cm), 120 ppb (1–2 cm), 88 ppb (2–

3 cm), 230 ppb (3–4 cm), 88 ppb (4–5 cm), 29 ppb (5-6 cm), and 17 ppb (6–7 cm). None of the DCBs were detected in the 7–8 cm sediment core. Chapman et al. (1996a, 1996b) also reported detecting 1,4-DCB in sediments collected around the diffuser of a large marine municipal sewage discharge outfall at Macaulay Point in Victoria, Canada. Sediment quality guidelines are set by the government to protect indigenous sediment-dwelling organisms. 1,4-DCB was detected at concentrations exceeding sediment quality guidelines (110 μg/kg [ppb] dry weight) and showed a distinctive concentration gradient, which peaked at the outfall at concentrations up to 1,710 ppb dry weight and decreased with increasing distance from the outfall. The authors attributed the source of the 1,4-DCB in the relatively untreated municipal sewage effluent to the extensive use of toilet block deodorizers.

In a recent study conducted in England, Wang and Jones (1994b) analyzed the chlorobenzene content of contemporary sewage sludge collected from 12 waste water treatment plants. Most of the plants surveyed received waste water from urban and industrial effluent and all of the sewage-treatment plants used primary treatment. 1,2- and 1,4-DCB were detected in 100% of the samples tested. 1,3-DCB was detected in 75% of the samples tested. Concentrations of 1,2-DCB ranged from 71.3 to 4,110 μg/kg (ppb) dry weight (3.57–152 ppb wet weight). For 1,2-DCB, the mean and median concentrations for the 12 plants were 877 and 237 ppb (dry weight), respectively. The authors reported that except for the monochlorobenzenes, 1,2-DCB had the highest concentration in the industrial sludges. This was believed to be the result of industrial uses of 1,2-DCB as a solvent, cleaner, degreaser, polish, and deodorant. Concentrations of 1,3-DCB ranged from below the detection limit to 467 μg/kg (ppb) dry weight (from below the detection limit to 13.5 ppb wet weight). For 1,3-DCB, the mean and median concentrations for the 12 plants were 82.3 and 30 ppb (dry weight), respectively. Concentrations of 1,4-DCB ranged from 561 to 2,320 μg/kg (ppb) dry weight (21.9–187 ppb wet weight). For 1,4-DCB, the mean and median concentrations for the 12 plants were 1,310 and 1,250 ppb (dry weight), respectively. The authors also reported that 1,4-DCB was the most abundant compound detected (exclusive of the monochlorobenzenes) and was detected at higher concentrations in the urban sludges compared to the sludges dominated by industrial sources. The authors believe that this was a result of the extensive use of the compound in moth repellent crystals, insecticides, germicides, and space deodorants. Since 1,4-DCB also has industrial uses, the absolute content of this compound was not lower in the industrial sludges as compared to the urban sludges. The authors also found that the 1,4-DCB content and that of other chlorobenzene compounds in sewage sludges from the same treatment plant were consistent over time. Wang et al. (1995) further reported that at a site in Woburn, England, sewage sludge applied to agricultural land from 1942 to 1961 contained 1,2-DCB concentrations of ND to 126 ppb (mean, 17.4 ppb; median, 6.60 ppb), 1,3-DCB concentrations of ND to 101 ppb (mean, 17.4 ppb; median, 6.60 ppb), and 1,4-DCB

concentrations of 7.76–71.8 ppb (mean, 29.8 ppb; median, 25.5 ppb). These authors found that while concentrations of the other chlorobenzenes remained stable during the 1960s after the sludge applications were halted in 1961, the concentrations of 1,4-DCB in both the sludge-amended and control soils actually increased. The authors concluded that the 1,4-DCB could have increased in both soil plots as a result of pesticide applications since 1,4-DCB was often found as an impurity in many organochlorine pesticides or by atmospheric deposition of airborne emissions from industrial facilities or municipal waste incinerators.

6.4.4 Other Environmental Media

DCBs have been detected in meat, poultry, fish, and other types of foodstuffs. Pork meat has reportedly been tainted with a disagreeable odor and taste as a result of the use of deodorant blocks in pig stalls (EPA 1980a; IARC 1982). Eggs also have been similarly tainted after hens were exposed to 20–30 mg/m^3 (3.3–5.0 ppm) of 1,4-DCB (IARC 1982). 1,4-DCB was detected in 69 out of 234 table-ready food items from the FDA's total diet study at concentrations ranging from 4.26 to 114 ppb (mean=10.7 ppb) (Heikes et al. 1995). 1,2-DCB was detected in 45 of the 234 food items at concentrations ranging from 7.80 to 24.4 ppb (mean=9.47 ppb). 1,3-DCB was detected in 6 of the food items at concentrations ranging from 5.31 to 9.76 ppb (mean=7.36). The highest level food items were chocolate chip cookies (1,4-DCB), cake doughnuts (1,2-DCB), and sandwich cookies (1,3-DCB). Page and Lacroix (1995) detected 1,4-DCB in both noncitrus based soft drinks and 10% butterfat cream at 0.1 μg/kg during a study of contaminants in Canadian foods. 1,4-DCB concentrations in different brands of butter, margarine, and peanut butter were 1.3–2.7, 12.2–14.5, and 1.2–8.8 μg/kg, respectively. Flour contained 1,2-DCB at 1.1 μg/kg and 1,4-DCB at 7.3 μg/kg, while pastry mix contained these isomers at concentrations of 1.0 and 22.0 μg/kg, respectively. Fresh food composites grown in Ontario, Canada were tested for the presence of DCBs (detection limits=0.0001 μg/g) as well as other contaminants (Davies 1988). Only 1,3-DCB was detected in fruit and root vegetables at concentrations of 0.0044 and 0.0011 μg/kg, respectively, while 1,2-DCB was the only isomer detected in the eggs/meat food group at a concentration of 0.0018 μg/kg. Both 1,3- and 1,4-DCB were detected in milk at concentrations of 0.00014 and 0.00055 μg/kg, respectively. None of the DCBs in this study were detected in leafy vegetables. The concentrations of 1,4-DCB in retail vegetables from the United Kingdom were 0.198 μg/kg (carrot cores), 0.416 μg/kg (carrot peels), 0.224 μg/kg (potato peels), 0.214 μg/kg (cauliflower stems), 0.529 μg/kg (cauliflower flowers), 0.237 μg/kg (inner lettuce leaves), and 0.118 μg/kg (outer lettuce leaves) (Wang and Jones 1994d). 1,2- and 1,3-DCB were detected only in potato cores at 0.328 and 0.096 μg/kg, respectively.

All three DCB isomers were detected in lake and rainbow trout from the Great Lakes at concentrations ranging from 0.3 to 1 ppb for 1,2-DCB, from 0.3 to 3 ppb for 1,3-DCB, and from 1 to 4 ppb for 1,4-DCB, (Oliver and Nicol 1982a). DCBs were detected in biota collected in the vicinity of an industrial outfall in the Calcasieu River estuary, Louisiana (Pereira et al. 1988). The concentrations of 1,2-, 1,3-, and 1,4-DCB in catfish ranged from not detected to 0.11 ppm, from 0.03 to 0.19 ppm, and from 0.17 to 0.47 ppm, respectively. The concentrations of DCBs in Atlantic croakers, blue crabs, spotted sea trout, and blue catfish collected from the Calcasien River estuary were 0.08, 0.26, 0.06, and 0.06 ppm, respectively for 1,2-DCB, 0.19, 0.356, 0.09, and 0.12 ppm, respectively, for 1,3-DCB, and 0.24, 0.60, 0.90, and 2.5 ppm, respectively, for 1,4-DCB. Chung (1999) detected 1,4-DCB in the leg meat, body meat, and carapace meat of *Charybdis feriatus*, a popularly consumed edible crab in Asia, at concentrations of 0.5, 0.6, and 5.1 ppm, respectively. DCBs were detected in the edible tissue of various species of trout, nase, whiting, mullet, and pilichard fresh water fish from rivers in Slovenia and the Gulf of Triest, Yugoslavia (Jan and Movnersic 1980). 1,4-DCB concentrations in these fish ranged from trace to 0.45 ppb, while 1,2-DCB concentrations ranged from trace to 1.14 ppb. The mean upper limit of 1,4,-DCB concentrations detected in livers of flatfish (Dover sole) collected off Los Angeles, California, was <77 ppb wet weight; the mean upper limit of concentrations found in muscle tissue was <7 ppb (Young and Heesen 1978). 1,2-DCB was also detected in these fish at mean liver concentrations at or below 4.0 ppb (Young et al. 1980). Concentrations of 1,4-DCB reported in mackerel from Japanese coastal water ranged up to 0.05 ppm wet weight (50 ppb) (EPA 1980a; IARC 1982). Jori et al. (1982) reported that 1,4-DCB has been detected in carp at 0.1 ppm and in farmed fish at 0.04 ppm.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Inhalation is the predominant route of exposure to DCBs for the general population. According to data from the TEAM study, which includes exhaled breath measurements from about 800 individuals, 1,4-DCB was found in 44–100% of air and breath samples from several U.S. locations, and indoor air levels were up to 25 times higher than ambient outdoor levels for DCB (1,3- and 1,4-DCB) (Wallace et al. 1986b). Mean concentrations of 1,3- and 1,4-DCB measured together in breath samples collected in New Jersey and California ranged from 2.9 to 8.1 $\mu g/m^3$ (Wallace 1986b). Median concentrations of these isomers in breath samples from New Jersey, California, North Dakota, and North Carolina ranged from 0.3 to 1.3 $\mu g/m^3$ (Wallace et al. 1987, 1996). 1,2-DCB was detected above quantifiable limits (0.2–2 $\mu g/m^3$) in only 2% of the breath samples collected in New Jersey (Wallace et al. 1986c). Mean 1,2-DCB concentrations ranged from 0.08 to 0.1 $\mu g/m^3$ in breath samples collected in California (Wallace

et al. 1988). The EPA has estimated that adult exposure to 1,4-DCB is about 35 μg/day, based on a mean ambient air concentration of 1.6 μg/m^3 (0.27 ppb) (EPA 1985a). In a separate study, average intake values for persons exposed to 1,2- and 1,3-DCB were estimated to be 1.8 and 0.8 μg/day, respectively, based on the concentrations of these substances in ambient outdoor air samples from seven large cities in the United States and a total air intake of 23 m^3/day (Singh et al. 1981a, 1981b). Inhalation exposure to 1,4-DCB may be considerably higher indoors where space deodorants or moth repellents that contain this chemical are used. Indoor inhalation exposure of the general population to 1,2- or 1,3-DCB is not expected to be important since these substances are not used in household and consumer products to the extent that 1,4-DCB is. However, one study reported that 1,3-DCB was detected in the air from a university art building where there is heavy use of printmaking solvents. Mean concentrations of 1,3-DCB were 0.4 μg/m^3 (median=0.8 μg/m^3) on the studio floor and 0.8 μg/m^3 (median below 0.5-1.5 ppb) on a non-use floor (Ryan et al. 2002). During this study, mean and median personal exposure concentrations for this compound were 2.0 and 2.3 μg/m^3, respectively.

Because water and food concentrations of DCBs are generally quite low, exposure from sources other than air is unlikely to be important. For example, drinking water containing 0.1 ppb 1,4-DCB would provide an additional intake of only 0.2 μg per day for an adult drinking 2 L of water per day. In the past, concentrations of all three DCB isomers have been detected in some freshwater fish from the Great Lakes region (Oliver and Nicol 1982a). In addition, concentrations of 1,2- and 1,4-DCB have been found in marine fishes, especially in areas near effluent discharges (Young and Heesen 1978; Young et al. 1980). However, more recent information on concentrations in edible fish and shellfish tissues is lacking.

Results of the National Human Adipose Tissue Survey (NHATS) conducted in 1982, which estimated the general population exposure to toxic organic chemicals, found that 1,4-DCB was detected in 100% of 46 composite human adipose tissue specimens analyzed at levels ranging from 12 to 500 ppb while 1,2-DCB was detected in 63% of the 46 specimens at levels ranging from <0.1–2 ppb (EPA 1986f, 1989d). These measurements indicate widespread exposure of the general population to DCBs. Using the same data, ranks for each of the 9 census regions were assigned according to the composite sample concentrations for 1,2- and 1,4-DCB or the means of multiple composite sample concentrations (Phillips and Birchard 1991). These authors reported that exposure to 1,4-DCB was highest for children (aged 0–14 years) living in the west south central (Arkansas, Louisiana, Oklahoma, and Texas), east south central (Kentucky, Tennessee, Alabama, and Mississippi), and south Atlantic regions (Delaware, Maryland, the District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, and Florida); for 15- to 44-year-olds, exposure was highest in the south Atlantic, middle Atlantic (New Jersey, New York,

and Pennsylvania), and east north central regions (Illinois, Indiana, Michigan, Ohio, and Wisconsin); and for adults 45 years and older, exposure was highest nationally in the east south central, west south central, and east north central regions. Exposure to 1,2-DCB was highest for children (0–14 years) living in the New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, and Connecticut), east north central, and west north central regions (Minnesota, Iowa, Missouri, Nebraska, Kansas, North Dakota, and South Dakota); for 15- to 44-year-olds, exposure was highest in the New England, mid Atlantic, and Pacific regions (California, Hawaii, Washington, Oregon, and Alaska); and for adults 45 years and older, exposure was highest nationally in the mid Atlantic, west north central, and west south central regions.

Table 6-10 summarizes concentrations of 1,4-DCB in blood samples from various studies. Morita and Ohi (1975) found that 1,4-DCB was present in all 34 adipose tissue and 6 blood samples taken from residents of the Tokyo, Japan metropolitan area. 1,4-DCB concentrations in the adipose tissue samples ranged from 0.2 to 11.7 ppm in the adipose tissue samples with an average concentration of 2.3 ppm and from 4 to 16 ng/ml (ppb) in the blood samples with an average concentration of 9.5 ng/mL (ppb). 1,2-DCB was detected in paired blood and biopsy fat samples obtained from 25 patients (7 male and 18 female) from British Columbia, Canada (Mes 1992). Median concentrations in whole blood, biopsy fatty tissue, blood lipids, and adipose tissue were <3.12, 28.1, <3, and 38 ppb, respectively. Maximum concentrations of 1,2-DCB in these media were 14.29, 154.5, 20,005, and 194 ppb, respectively.

Concentrations of 1,4-DCB in blood samples of 48 individuals in Alaska during February 1995 ranged from below the limit of detection (0.040 ppb) to 7.10 ppb with median values ranging from 0.02 to 0.04 ppb (Backer et al. 1997). During the Third National Health and Nutrition Evaluation Survey (NHANES III), 1,4-DCB was detected in 94.6% of 1,100 blood samples at a median concentration of 0.33 μg/L and a 95th percentile value of 9.2 μg/L (Buckley et al. 1997). Blood samples collected from July 1995 to May 1997 during the National Human Exposure Assessment Survey (NHEXAS) in EPA Region 5 (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) contained 1,4-DCB (Pellizzari et al. 2001). It was detected in approximately 80 out of 145 samples with a median concentration of 0.10 ppb, an arithmetic mean concentration of 0.38 ppb, and a maximum concentration of 45 ppb (Bonanno et al. 2001). Ashley et al. (1994, 1996) reported a mean blood level of 1,4-DCB of 1.9 ppb (median 0.33 ppb) in 1,037 samples collected from a reference group of nonoccupationally exposed individuals. Concentrations of VOCs in blood samples from a group of 126 nonsmokers and 42 smokers were also studied (Ashley et al. 1995). These authors found that mean 1,4-DCB blood levels were 3.2 ng/L (ppb) (median, 0.45 ppb; range ND–96 ppb) for nonsmokers and 2.2 ppb (median, 0.47 ppb;

Table 6-10. Concentrations of 1,4-Dichlorobenzene in Blood Samples

Test subjects	Range (ppb)	Median (ppb)	Mean (ppb)	Reference
British Columbia, Canada (n=25)	≤14.29	<3.12		Mes 1992
Alaska, United States (n=48)	<0.040[a]–7.10	0.02–0.04		Backer et al. 1997
NHANES III (n=1,100)		0.33		Buckley et al. 1997
EPA Region 5 (n=145)	≤45	0.10	0.38	Pellizzari et al. 2001
Non-occupationally exposed individuals (n=1,037)		0.33	1.9	Ashley et al. 1994, 1996
Nonsmokers (n=126)	ND–96	0.45	3.2	Ashley et al. 1995
Smokers (n=42)	ND–17	0.47	2.2	Ashley et al. 1995
Residents of the Love Canal area, Niagara Falls, New York	0.15–68			EPA 1985a
World Trade Center firefighters present during the collapse (n=148)			0.274	Edelman et al. 2003
World Trade Center firefighters arriving within 2 days of the collapse (n=142)			0.289	Edelman et al. 2003
World Trade Center special operations command individuals (n=95)			0.343	Edelman et al. 2003
Other World Trade Center firefighters			0.231	Edelman et al. 2003
SHIELD—children in Minneapolis, Minnesota (n=134)		0.21	4.22	Sexton et al. 2005
Adults in the United States (n=1,000)	≤49	0.33	2.1	Hill et al. 1995

[a]Below the limit of detection

range, ND–17 ppb) for smokers. Blood levels of 1,4-DCB were not dependent on whether the subject was from the smoking or control group. All three DCB isomers have been detected in blood samples from residents of the Love Canal area in Niagara Falls, New York (IARC 1999). DCB concentrations in blood samples from nine Love Canal residents ranged from 0.15 to 68 ppb (EPA 1985a). 1,4-DCB concentrations (geometric mean) in blood samples collected from firefighters responding to the World Trade Center fire and collapse were 0.274 μg/L for 148 firefighters who were present during the collapse and 0.289 μg/L for 142 firefighters who arrived after the collapse (within 2 days) (Edelman et al. 2003). The mean concentrations in the blood of 95 special operations command individuals were 0.343 μg/L compared to 0.231 μg/L in the blood of other firefighters.

Hill et al. (1995) analyzed both blood and urine samples of 1,000 adults in the United States. These authors reported that 96% of the individuals in the study had detectable concentrations of 1,4-DCB in their blood and 98% had detectable concentrations of 2,5-dichlorophenol (the metabolite of 1,4-DCB) in their urine. 1,4-DCB levels in the blood ranged up to 49 μg/L (ppb), with median and mean concentrations of 0.33 ppb and 2.1 ppb, respectively. Urinary 2,5-dichlorophenol concentrations ranged up to 8,700 μg/L (ppb), with median and mean concentrations of 30 ppb and 2,000 ppb, respectively. There was a highly significant correlation ($p<0.0001$) between 2,5-dichlorophenol in the urine and 1,4-DCB in the blood. The authors concluded that 1,4-DCB is a common, worldwide environmental contaminant. Metabolites of 1,2-DCB (2,3- and 3,4-dichlorophenol and 3,4- and 4,5-dichlorocatechol) have been detected in the urine of chemical factory workers at unspecified concentrations (Kumagai and Matsunaga 1995, 1997). These workers had been exposed to 1,2-DCB used as a solvent during the work shift prior to sample collection.

DCB (all isomers) was identified in 100% of 42 samples of human breast milk collected in five urban areas of the United States at concentrations of 0.04–68 ppb (Erickson et al. 1980). DCB (all isomers) was identified in human breast milk in 8 of 12 women who were residents of Bayonne, New Jersey (6 women), Jersey City, New Jersey (2 women), Bridgeville, Pennsylvania (2 women), and Baton Rouge, Louisiana (2 women); however, concentrations were not specified (Pellizzari et al. 1982). DCB (all isomers) was identified in breast milk samples collected from five different regions across Canada in 1982 (Mes et al. 1986). 1,2-DCB was identified in 97% of the 210 samples collected with mean and maximum milk concentrations of 3 and 29 ppb, respectively and mean and maximum concentrations in milkfat of 84 and 890 ppb, respectively. 1,3- and 1,4-DCB were identified together in 100% of the 210 samples collected with mean and maximum milk concentrations of 6 and 75 ppb, respectively and mean and maximum concentrations in milkfat of 161 and 4,180 ppb, respectively. Mean concentrations

of 1,2-, 1,3-, and 1,4-DCB in breast milk samples collected in Slovenia, Yugoslavia in 1981 were 9, <5, and 25 μg/kg, respectively (Jan 1983). 1,2- and 1,4-DCB concentrations in the milkfat of these samples were 230 and 640 μg/kg, respectively.

Occupational exposure to DCBs may be important in several industries associated with the production of various chlorobenzene compounds. Workers may be exposed to DCBs during production, processing, and industrial use of these compounds, including the production and handling of products that contain these compounds (IARC 1999). Workplace air levels of 1,4-DCB ranging up to 4,350 mg/m^3 (724 ppm) were measured at facilities producing or using the compound (IARC 1982). A summary of the levels of 1,4-DCB detected in various occupational settings is presented in Table 6-7. Currently, workers in the industries identified in Table 6-7 are likely to have the highest potential for exposure to 1,4-DCB. Levels of 1,2- and 1,3-DCB in workplace air were not found. NIOSH estimated that about 34,000 workers were potentially exposed to 1,4-DCB, about 92,000 workers were potentially exposed to 1,2-DCB, and about 400 workers were potentially exposed to 1,3-DCB in the early 1980s (NOES 1990).

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).

There have been no measurements of the levels of DCBs in amniotic fluid, meconium, cord blood, or neonatal blood to investigate prenatal exposure. However, DCBs have been detected in full-term placentas collected from five regions of the Slovak Republic (Reichrtova et al. 1999, 2001). Over 40 placentas were sampled from each region. DCB concentrations measured in these placentas are provided in Table 6-11. DCBs were found most frequently in placentas from Bratislava, Slovakia

Table 6-11. Dichlorobenzene Concentrations (μg/kg) in Human Placentas from Five Slovak Regions

Region	1,2-DCB			1,3- and 1,4-DCB		
	% Detected	Median	Maximum	% Detected	Median	Maximum
1. Bratislava	82	0.8	46.9	81	1.4	218.0
2. Nove Zamky	75	0.1	1.3	55	0.2	10.2
3. Spisska Nova Ves	10	0.0	0.2	34	0.0	45.0
4. Kosice	10	0.0	0.8	40	0.0	99.5
5. Stara Lubovna	82	8.1	64.3	79	0.8	26.9

Source: Reichrtova et al. 1999, 2001

(industrial region–petrol, pesticide, and rubber industries), Nove Zamky, Slovakia (agricultural region with high use of fertilizers), and Stara Lubovna, Slovakia (partially agricultural rural region with increasing cross-county traffic). DCBs were found less frequently in samples from Spisska Nova Ves and Kosice (industrial regions with heavy metal pollution).

Consumption of human milk can potentially expose nursing infants to DCB. DCB (all isomers) was detected in 100% of 42 samples of human milk collected in five urban areas of the United States at concentrations ranging from 0.04–68 ppb; however, concentrations of the individual isomers were not specified (Erickson et al. 1980). DCB (all isomers) was also identified in human breast milk in 8 of 12 women who were residents of Bayonne, New Jersey (6 women); Jersey City, New Jersey (2 women); Bridgeville, Pennsylvania (2 women); and Baton Rouge, Louisiana (2 women); however, concentrations of the individual isomers were not specified (Pellizzari et al. 1982). DCB (all isomers) were identified in breast milk samples collected from five different regions across Canada in 1982 (Mes et al. 1986). 1,2-DCB was identified in 97% of the 210 samples collected with mean and maximum milk concentration of 3 and 29 ppb, respectively, and mean and maximum concentrations in milkfat of 84 and 890 ppb, respectively. 1,3-and 1,4-DCB were identified together in 100% of the 210 samples collected with mean and maximum milk concentrations of 6 and 75 ppb, respectively, and mean and maximum concentrations in milkfat of 161 and 4,180 ppb, respectively. Mean concentrations of 1,2-, 1,3-, and 1,4-DCB in breast milk samples collected in Slovenia, Yugoslavia in 1981 were 9, <5, and 25 μg/kg, respectively (Jan 1983). 1,2- and 1,4-DCB concentrations in the milkfat of these samples were 230 and 640 μg/kg, respectively.

Children are exposed to 1,4-DCB primarily by inhalation of vapors from toilet deodorants, moth proofing crystals, and moth balls used in the home or by consumption of moth balls. Consumption of DCBs in foods (see Section 6.4.4) and drinking water (see Section 6.4.2) contaminated with DCBs is thought to be a minor exposure pathway. There have been no body burden measurements made on children.

The National Human Adipose Tissue Survey (NHATS) conducted in 1982, estimated general population exposure to a variety of toxic organic chemicals. 1,4-DCB was detected in 100% of 46 composite human adipose tissue specimens analyzed at levels ranging from 12 to 500 ppb, whereas 1,2-DCB was detected in 63% of the 46 specimens at levels ranging from <0.1 to 2 ppb (EPA 1986f, 1989d). These measurements indicate widespread exposure of the general population including children (aged 0–14 years) to DCBs. Using this same data, ranks for each of the nine census regions were assigned according to the composite adipose tissue concentration of 1,4-DCB or the mean of multiple adipose composite samples

(Phillips and Birchard 1991). These authors reported that exposure to 1,4-DCB based on adipose tissue levels was highest nationally for children (aged 0–14 years) in the west south central (Arkansas, Louisiana, Oklahoma, and Texas), east south central (Kentucky, Tennessee, Alabama, and Mississippi), and south Atlantic regions (Delaware, Maryland, the District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia and Florida) as compared to other areas of the United States. Exposure to 1,2-DCB was highest for children (0–14 years) living in the New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, and Connecticut), east north central (Illinois, Indiana, Michigan, Ohio, and Wisconsin), and west north central regions (Minnesota, Iowa, Missouri, Nebraska, Kansas, North Dakota, and South Dakota). 2,5-Dichlorophenol, a metabolite of 1,4-DCB, and 3,4-dichlorophenol, a metabolite of 1,2-dichlorophenol, were detected in urine samples from 197 Arkansas children (Hill et al. 1989). 2,5-Dichlorophenol was detectable in 96% of the samples with median and maximum concentrations of 9 and 1,200 ppb, respectively. 3,4-Dichlorophenol was detectable in 6% of the samples with median and maximum concentrations of <1 ppb (detection limit) and 9 ppb.

Childhood exposures can be reduced by appropriate use of 1,4-DCB-containing compounds in the home and appropriate supervision of young children. Small children, because of their hand-to-mouth activity, may receive significant exposure from ingestion of 1,4-DCB. Moth balls look like candy; a young child may be tempted to eat them. Accidental poisoning by consumption of this household chemical is likely to occur if the moth balls and/or crystals are placed in a location easily accessed by children and under conditions where children are not properly supervised. It is also important that children not be allowed to play around toilet deodorants and air fresheners unsupervised. Since some 1,4-DCB is applied as a crystalline form, children may be exposed dermally, orally (in hand-to-mouth activities), or by inhalation of dust particles or vapors while playing on floors or carpeting where 1,4-DCB-contaminated particles may have fallen after moth proofing activities in the home. It is important that children not be allowed entry into 1,4-DCB-treated storage areas until the moth crystals have sublimated and the vapors have dissipated.

Children living in homes of adults that are occupationally exposed to DCBs must not be exposed to the contaminated work clothes or shoes of adults (DHHS 1995). While the vast majority of occupational exposures are likely to be by inhalation of DCB vapors by workers, a potential route of exposure to other members of the worker's family including children may occur if DCB contaminated work clothes are brought home for laundering. The chemical contamination on the clothing may then vaporize releasing DCBs into the indoor air of the workers' home. Occupational protection statements for the end use DCB products state that individuals occupationally exposed to these products should take off all wet or

contaminated work clothes and shoes and shower using soap and water, and then put on clean clothes (NIOSH 1997). Although no studies were found that investigated this pathway of exposure, it is conceivable that poor hygiene practices among occupationally exposed adults could potentially result in domestic exposures of other family members to DCBs carried home on work clothes and subsequently to the vapors released.

As discussed in Section 6.5 of this profile, inhalation of indoor air is the major exposure route for both adults and children in the general population; however, several other minor pathways may also result in exposure. Like adults, children living in proximity to hazardous waste sites may be exposed to DCBs in contaminated groundwater. If residential wells are the primary source of drinking water, this may pose a risk to human health by consumption of contaminated water and by increased inhalation of, and dermal contact with DCBs during showering and bathing.

Little information on the levels of DCB concentrations in infant and toddler foods and in baby formula was located. Page and Lacroix (1995) analyzed a variety of beverage and food samples for 32 different volatile contaminants, including 1,4-DCB, and found residue levels to be quite low (range, 0.1–22 ppb). Soft drink samples contained 0.1 μg/kg (ppb), while cream with 10% butterfat, butter, margarine, peanut butter, flour, and pastry mix contained concentrations of 0.1, 1.3–2.7, 12.2–14.5, 1.2–8.8, 7.3, and 22 ppb, respectively. 1,2-, 1,3-, and 1,4-DCB were detected in 45, 6, and 69 out of 234 table-ready food items from the FDA's total diet study, respectively. Positive detections of all three isomers had concentrations within a range of 4.26 to 114 ppb (Heikes et al. 1995). No information was located to determine whether children differed in their weight-adjusted intake of 1,4-DCB.

There are some parental exposures to DCBs that might result in potential exposures of children to this chemical. DCBs are not genotoxic and, thus, there should be no concern about exposure to parental germ cells (see Table 3-3 and 3-4 for further information). Additional information on the genotoxicity of these compounds can be found in Section 3.7, Children's Susceptibility. Because DCBs have been widely detected in samples of human adipose tissue, the potential exists for these compounds to be stored in maternal tissues from preconception exposures and mobilized during gestation or lactation so that the developing fetus or embryo or nursing infant is exposed even after external exposure to the mother has ceased. Like all organochlorine compounds, DCBs are stored in fatty tissue. 1,4-DCB was detected in 100% of adipose tissue samples of adults and children analyzed as part of the National Adipose Tissue study (EPA 1986f). As previously mentioned, there have been measurements of all DCB isomers

(combined) in human breast milk (Erickson et al. 1980; Pellizzari et al. 1982). For additional information on developmental effects of this compound, please see Section 3.7, Children's Susceptibility.

During the Minnesota Children's Pesticide Exposure Study, 1,4-DCB was detected above 0.2 μg/m^3 in 70 of 73 personal air samples, 83 of 101 indoor air samples, and 42 of 100 outdoor air samples collected from households with children (Adgate et al. 2004). The mean concentration of 1,4-DCB was 1.4 μg/m^3 in the personal air samples, 0.9 μg/m^3 in the indoor air samples, and 0.3 μg/m^3 in the outdoor air samples. During the School Health Initiative: Environment, Learning, Disease (SHIELD) study, the median concentrations of 1,4-DCB measured in the outdoor home air, indoor school air, indoor home air, and personal air of 113 children from two inner-city schools in Minneapolis, Minnesota were 0.1, 0.5, 0.7, and 1.0 μg/m^3, respectively, during the winter and 0.2, 0.5, 0.9, and 1.3 μg/m^3, respectively, during the summer (Adgate et al. 2004). The mean, median, and 95th percentile concentrations of 1,4-DCB measured in the blood of 134 children during the SHIELD study were 4.22, 0.21, and 24.5 μg/m^3, respectively (Sexton et al. 2005).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to DCBs (see Section 6.5), several groups within the general population have potentially higher exposures (higher than background levels) to DCBs than the general population. These populations include individuals living near sites where DCB are produced or used in manufacturing and sites where DCBs are disposed.

Those individuals living or working near industrial facilities or hazardous waste sites with higher than average levels of DCBs in the air would have the potential for above-average exposures. In addition, individuals using space deodorants (air fresheners), toilet block deodorants, or moth repellents (moth balls or crystal) containing 1,4-DCB in their homes have the potential for high exposure to this compound (Scuderi 1986). Indoor air concentrations resulting from the use of these products in bathrooms and closets have been measured at levels up to 1.3 mg/m^3 (0.22 ppm) (Scuderi 1986).

Individuals living in proximity to hazardous waste sites may also be exposed to DCB by contaminated groundwater. If residential wells are the primary source of drinking water, this may pose a risk to human health by consumption of contaminated water and by increased inhalation of and dermal contact with DCBs during showering and bathing.

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 dichlorobenzenes 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 dichlorobenzenes.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of the DCBs are sufficiently well characterized to allow estimation of its environmental fate (Amoore and Hautala 1983; Chiou et al. 1983; Howard 1989; Lide and Frederikse 1994; Newsom 1985; NFPA 1994; Sax and Lewis 1987; Schwartzenbach and Westall 1981; Verschueren 1983; Wilson et al. 1981). On this basis, it does not appear that further research in this area is required.

Production, Import/Export, Use, Release, and Disposal. Data on the production and uses of DCBs in the United States are available (CMR 1990; HSDB 2005; IRPTC 1985; SRI 1996; TRI03 2005). Incineration is the recommended disposal method for DCBs (HSDB 2005; IRPTC 1985). Disposal of this compound is controlled by federal regulations (HSDB 2005; IRPTC 1985). Available information appears to be sufficient for assessing the potential for release of, and exposure to, DCBs.

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 2003, became available in May of 2005. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The environmental fate of the DCBs has been well characterized. Their volatilization into air from other media, reaction with hydroxyl radicals in the atmosphere, transport through soil, and biodegradation by water and soil microorganisms seem to be well understood (Bouwer and McCarty 1982, 1983, 1984; Chiou et al. 1983; Cuppitt 1980; EPA 1985d; Garrison and Hill 1972; Howard 1989; Ligocki et al. 1985; Newsom 1985; Schwartzenbach and Westall 1981; Singh et al. 1981a, 1981b; Scuderi 1986; Spain and Nishino 1987; Tabak et al. 1981; Wakeham et al. 1983; Wang and Jones 1994a, 1994b, 1994c; Wilson et al. 1981). Volatilization, sorption, biodegradation, and bioaccumulation appear to be competing processes for the removal of DCBs from water (Spain and Nishino 1987). Additional data on the rates of these reactions under various environmental conditions would be useful, but do not appear to be essential to understand the behavior of DCBs in the environment.

Bioavailability from Environmental Media. DCBs have been shown to be well absorbed by laboratory animals via inhalation and oral exposure (Hawkins et al. 1980; Kimura et al. 1979). No information has been located regarding absorption by the dermal route. Although no information has been located on the absorption of this substance from breathing contaminated air or ingesting DCBs that are contained in soil or plant material are expected to be well absorbed from these media. It would be useful to have information on whether, and to what extent, absorption of DCBs can occur as a result of dermal contact with soil or from swimming in surface water or bathing or showering in groundwater that contains DCBs.

Food Chain Bioaccumulation. Bioconcentration of DCBs has been documented for several aquatic species (ASTER 1995; Chiou 1985; Oliver and Nicol 1982a; Oliver and Niimi 1983). Based on the relatively high K_{ow}, it appears that bioaccumulation does occur (Leo et al. 1971). Oliver and Nicol (1982a) measured concentrations of chlorobenzenes in sediments, water, and selected fish from the Great Lakes. Their limited fish analyses indicate that chlorobenzenes, including DCBs, are bioconcentrated by fish, but to a much smaller extent than compounds such as DDT or PCBs. DCBs have also been shown to be accumulated by terrestrial plants (Wang et al. 1996). No data were located on biomagnification of DCBs through terrestrial or aquatic food chains. Additional information on bioconcentration of DCBs by commercially important fish, shellfish, and plant species and biomagnification would be helpful in evaluating the potential importance of food chain bioaccumulation to human exposure.

Exposure Levels in Environmental Media. Several studies are available documenting levels of DCBs in indoor and ambient outdoor air, water, and soil and sediments in rural, suburban, and urban areas and in the environs of hazardous waste sites (Bozzelli and Kebbekus 1979; Coniglio et al. 1980;

Dressman et al. 1977; Elder et al. 1981; Fellin and Otson 1994; Harkov et al. 1984, 1985; Hauser and Bromberg 1982; IARC 1982; IJC 1989; Kostianen 1995; LaRegina et al. 1986; Oliver and Nicol 1982a; Page 1981; Scuderi 1986; Shah and Heyerdahl 1988; Staples et al. 1985; Wallace et al. 1986a, 1986b, 1989). It would be valuable to have more recent monitoring data to better estimate the potential for current human exposure levels from these media, especially in the vicinity of hazardous waste sites.

Although there is little information on DCB levels in food (IARC 1982; Oliver and Niimi 1983; Page and Lacroix 1995), it does not appear that this is an important source of human exposure. However, additional data on DCB levels in foodstuffs, especially commercially important fish, shellfish, and plants, would be useful to confirm this assumption.

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

Exposure Levels in Humans. Detection of DCBs in breath, adipose tissue, breast milk, and blood can be used as indicators of human exposure (Ashley et al. 1994, 1995; EPA 1986f, 1989d; Erickson et al. 1980; Hill et al. 1995; Pellizzari et al. 1982; Wallace et al. 1986b). Levels of DCBs in breath appear to provide rough estimates of recent preceding exposure (Wallace et al. 1986b), while levels in adipose tissue may be useful to indicate less recent past exposure (EPA 1986f, 1989d). The level of 2,5-dichlorophenol (a metabolite of 1,4-DCB) has also been reported in urine of 1,000 individuals (Hill et al. 1995), and is highly correlated to 1,4-DCB in blood. Additional data correlating levels in environmental media with human tissue levels, particularly for populations living in the vicinity of hazardous waste sites that contain DCBs, would be helpful in establishing levels of the chemical to which humans have been exposed. Additional monitoring data on the occupational exposure of workers to DCBs would be helpful. Additional studies reporting inhalation exposure through the use of toilet air fresheners and mothballs that contain DCBs would be useful.

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

Exposures of Children. Children, like all members of the general population, are exposed to DCBs primarily by inhalation. No exposure or body burden studies were specifically located related to children. Studies to quantify the amount of DCBs in amniotic fluid, meconium, cord blood, or neonatal blood

would be useful in assessing prenatal exposure. Maternal-fetal exposure should be evaluated since there is some genotoxic potential. Studies on the amount of the DCBs specifically in breast milk would be useful in assessing exposures in nursing infants. Although inhalation of 1,4-DCB is the most important exposure pathway in humans, consumption of moth crystals or moth balls by young children also may result in additional exposure of concern. It is not known whether children are different from adults in their weight-adjusted intake of 1,4-DCB. Studies on this topic with respect to inhalation and dietary intake are needed. Childhood exposure to this chemical can be decreased by the appropriate use of this compound particularly in the home and by appropriate supervision of young children. Education programs for parents and young children may be appropriate to reduce poisoning incidents. Studies on exposures of janitorial personnel and other occupationally exposed adults would also be helpful in determining the amount of 1,4-DCB that may accumulate on work clothes and whether crystalline particles of the toilet deodorants or moth crystal can be carried home on work clothing leading to additional domestic exposures from crystals and subsequently to vapors.

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 dichlorobenzenes were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

A search of Federal Research in Progress (FEDRIP 2005) identified one ongoing study that is related to dichlorobenzenes. James Heist of Ftc Acquisition Corporation is being funded by the Air Force to study material recycling and waste minimization using a freeze crystallization process. Dichlorobenzenes are among the substances for which recycling via this method will be considered.

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring dichlorobenzenes, its metabolites, and other biomarkers of exposure and effect to dichlorobenzenes. 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

Methods are available for measuring levels of DCBs in blood, urine, tissue, and breath. Representative methods are summarized in Table 7-1. Methods include sample collection, preparation, cleanup, and determination. Sample preparation techniques are usually required to separate the compound of interest from the complex biological sample medium. Gas purge and solvent extraction are used most frequently to separate DCBs from blood, urine, and tissues. The breath matrix is relatively simple and does not require preparation steps; however, special techniques such as use of a spirometer are required to provide pure air for inhalation and a mechanism for collection of exhaled air. Gas chromatography (GC) is used most frequently to detect DCBs in biological materials. Detectors used to identify DCBs in biological materials include the electron capture detector (ECD) (Bristol et al. 1982; Jan 1983), the photoionization detector (PID) (Langhorst and Nestrick 1979), and mass spectrometry (MS) (Ashley et al. 1992; Michael et al. 1980). ECD and PID provide some selectivity, but confirmation using a different GC column or detector is often recommended. MS provides identification as well as quantitation of analytes.

Separation of DCBs from biological samples may be accomplished by extraction with hexane (Bristol et al. 1982; Jan 1983), or carbon tetrachloride (Langhorst and Nestrick 1979), or by purging with an inert gas and trapping on a sorbent material. Solvent extraction permits concentration, thereby increasing sensitivity, but the extraction solvents can interfere with the analysis, and evaporative losses can result in low recovery. Gas purge techniques may be static (headspace) or dynamic (purge-and-trap). The static

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

Sample matrix (analyte)	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (1,3-DCB)	Headspace purge; thermal desorption	cap. GC/MS	3 ng/mL	86.3	IARC Method 25; Pellizzari et al. 1985
Blood (model compounds)	Headspace purge; thermal desorption	cap. GC/MS	Low-ppb	86–120 (model compounds)	Michael et al. 1980
Blood (1,2-DCB)	Solvent extraction; silica gel column clean-up	GC/PID	3.6 ppb	85	Langhorst and Nestrick 1979
Blood (1,3-DCB)	Solvent extraction; silica gel column clean-up	GC/PID	2.8 ppb	82	Langhorst and Nestrick 1979
Blood (1,4-DCB)	Solvent extraction; silica gel column clean-up	GC/PID	3.0 ppb	89	Langhorst and Nestrick 1979
Blood (1,2-DCB)	Solvent extraction	GC/ECD	1.4 ppb	76.6	Bristol et al. 1982
Blood (1,3-DCB)	Solvent extraction	GC/ECD	1.3 ppb	74.5	Bristol et al. 1982
Blood (1,4-DCB)	Solvent extraction	GC/ECD	2 ppb	81.6	Bristol et al. 1982
Blood (1,2-DCB)	Purge and trap	cap. GC/MS	0.05 ppb	77–122	Ashley et al. 1992
Blood (1,3-DCB)	Purge and trap	cap. GC/MS	0.04 ppb	130–162	Ashley et al. 1992
Blood (1,4-DCB)	Purge and trap	cap. GC/MS	0.04 ppb	93–98	Ashley et al. 1992
Blood, urine (unspecified DCBs)	Purge-and-trap, thermal desorption cap	GC/MS	No data	No data	Barkley et al. 1980
Urine (1,2-DCB)	Solvent extraction; silica gen column clean-up	GC/PID	0.90 ppb	83	Langhorst and Nestrick 1979
Urine (1,3-DCB)	Solvent extraction; silica gen column clean-up	GC/PID	0.70 ppb	78	Langhorst and Nestrick 1979
Urine (1,4-DCB)	Solvent extraction; silica gen column clean-up	GC/PID	0.75 ppb	81	Langhorst and Nestrick 1979
Urine (model compounds)	Headspace purge; thermal desorption	cap. GC/MS	Low-ppb	48–110 (model compounds)	Michael et al. 1980

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

Sample matrix (analyte)	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue (model compounds)	Maceration; headspace purge; thermal desorption	cap. GC/MS	Low-ppb	13–80 (model compounds)	Michael et al. 1980
Human milk (chloro-benzene)	Headspace purge; thermal desorption	GC/MS	0.6	62.9	Erickson et al. 1980
Human milk (unspecified DCBs)	Solvent extraction; cleanup with sulfuric acid, Florisil	GC/ECD	No data	>80	Jan 1983
Adipose tissue (unspecified DCBs)	Solvent extraction; cleanup with sulfuric acid, Florisil	GC/ECD	No data	>80	Jan 1983
Tissue (1,3-DCB)	Maceration; headspace purge; thermal desorption	cap. GC/MS	6 ng/g	56.5	IARC Method 25; Pellizzari et al. 1985
Breath (unspecified DCBs)	Collection using a spirometer; adsorption on Tenax traps; thermal desorption cap	GC/MS	No data	No data	Barkley et al. 1980
Breath (1,4-DCB)	Collection into canisters using spirometer; cryofocussing; thermal desorption	cap. GC/MS-SIM	low-$\mu g/m^3$	49–80	Thomas et al. 1991

cap. = capillary; ECD = electron capture device; GC = gas chromatography; MS = mass spectrometry; PID = photo-ionization detector; SIM = selected ion monitoring

headspace technique is relatively simple, but may be less sensitive than the purge-and-trap method. The purge-and-trap method, while providing increased sensitivity, requires more complex instrumentation and may result in artifact formation (Seto 1994).

Although a variety of methods are available for determination of DCBs in blood, few are well characterized and validated. A method has been developed which utilizes headspace purge followed by thermal desorption of the trapped, purged analytes. DCBs are then determined by capillary GC/MS (Michael et al. 1980; Pellizzari et al. 1985). Recovery is very good (>85%) and detection limits are in the low-ppb range for model compounds (Michael et al. 1980; Pellizzari et al. 1985). A sensitive and reliable method for identification and quantitation of DCBs in samples of whole blood has been developed by Ashley and coworkers at the Centers for Disease Control and Prevention (CDC) (Ashley et al. 1992). The method involves purge-and-trap of a 10 mL blood sample with analysis by capillary GC/high resolution MS. Anti-foam procedures are utilized as well as special efforts to remove background levels of volatile organic compounds (VOCs) from reagents and equipment. The method is sensitive enough (ppt levels) to determine background levels of VOCs in the population. Percent recoveries were 77–122% for 1,2-DCB, 130–162% for 1,3-DCB, and 93–98% for 1,4-DCB.

Methods are available for monitoring DCBs in urine and tissues, particularly adipose tissue and mother's milk. Solvent extraction, silica gel column clean-up, and GC/ECD or GC/PID analysis has been used for urine (Langhorst and Nestrick 1979), mother's milk (Jan 1983), and adipose tissue (Jan 1983). Recovery is good (>80% recovery) and detection limits are in the low-ppb range (Jan 1983; Langhorst and Nestrick 1979). Headspace purge followed by capillary GC/MS analysis has been utilized for urine (Michael et al. 1980), mother's milk (Erickson et al. 1980), and tissue (Pellizzari et al. 1985). Recovery, where reported, is adequate (>60%) (Erickson et al. 1980), and detection limits are in the low-ppb range (Erickson et al. 1980).

Breath samples are usually collected through a spirometer onto a sorbent cartridge (Barkley et al. 1980) or into passivated canisters (Thomas et al. 1991). Analytes are concentrated cryogenically from a portion of the canister contents or after thermal desorption from the sorbent, then analyzed by GC/MS. Recovery of 1,4-DCB using Tenax cartridges was 86–101% and the detection limit was about 1 $\mu g/m^3$. The method is sufficiently sensitive and reliable for monitoring exposure to DCBs. Recovery for collection of 1,4-DCB in canisters was 49–80% and the detection limits were in the low-$\mu g/m^3$ range (Thomas et al. 1991). The spirometer system utilizing canisters is compact, and may be useful as a field screening method (Thomas et al. 1991).

7.2 ENVIRONMENTAL SAMPLES

Methods are available for determining DCBs in a variety of environmental matrices. A summary of representative methods is shown in Table 7-2. Validated methods, approved by agencies and organizations such as EPA, ASTM, APHA, and NIOSH, are available for air, water, and solid waste matrices. These methods for analysis of drinking water, waste water, and soil/sediment samples are included in Table 7-2. Many of the methods published by APHA and ASTM for water are equivalent to the EPA methods.

GC is the most widely used analytical technique for quantifying concentrations of DCBs in environmental matrices. Various detection devices used for GC include the flame ionization detector (FID), ECD, Hall electroconductivity detector (HECD), and PID. Confirmation using a second column is usually recommended. MS provides identification as well quantitation for GC analysis. Because of the complexity of the sample matrix and the usually low concentrations of VOCs in environmental media, sample concentration is generally required prior to GC analysis. Methods suitable for determining trace amounts of DCBs in aqueous and other environmental media include three basic approaches to the pretreatment of the sample: gas purge-and-trap technique, headspace-gas extraction, and extraction with solvent. Care must be taken during sample collection and processing to avoid evaporative losses. Contamination is another potential analytical problem and monitoring is required. 1,4-DCB is a relatively common chemical compound and can contaminate reagents and glassware.

Charcoal adsorbent is used for collection of DCBs in occupational air. The compounds are desorbed with carbon disulfide and analyzed by GC/FID. The method is sufficiently sensitive and reliable for determining occupational exposure to DCBs (NIOSH 1994).

Ambient air samples are collected on adsorbents such as Tenax (Wallace 1987), or multisorbent (Heavner et al. 1992; Oliver et al. 1996), or in passivated canisters (EPA 1988a). Tenax traps are thermally desorbed, concentrated cryogenically, and analyzed by capillary GC/MS (Wallace et al. 1987). Recovery is good (81–110%), precision for side-by-side samples is acceptable (9–45% RSD), and the detection limit is ≈1 $\mu g/m^3$ (Wallace 1987). Multisorbent traps may be solvent desorbed and analyzed by capillary GC/MS. Recovery and precision are good and detection limits as low as 0.019 ppb have been reported (Oliver et al. 1996). Collection of air samples in passivated stainless steel canisters is also widely utilized

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

Sample matrix (analyte)	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (1,2-DCB)	Collection on charcoal tubes; desorption with CS_2	GC/FID	0.01 mg/ sample[a]	±13.7	Method 1003 NIOSH 1994
Occupational air (1,4-DCB)	Collection on charcoal tubes; desorption with CS_2	GC/FID	0.01 mg/ sample[a]	±12.5	Method 1003 NIOSH 1994
Ambient air (VOCs including DCBs)	Collection in canisters; cryofocussing; thermal desorption	cap. GC with FID, ECD or MS	No data	No data	Method TO-14 EPA 1988a
Air-emission sources (selected compounds)	MM5 sampling train (condensate, filter, adsorbent); condensate, impinger and rinses, solvent extraction, evaporation; XAD-2 adsorbent and filters, Soxhlet extraction, concentration	cap. GC/MS	No data	-13 to -16	Method 0010 EPA 1994f
Air-emission sources (volatile organics)	VOST sampling train (sorbent traps); thermal desorption	GC/MS	No data	No data	Method 0030 EPA 1994h
Drinking water (1,2- and 1,3-DCB)	Purge and trap	GC/HECD; conf. on second col. or GC/MS	<0.01 μg/L for most VOCs	95	Method 502.1 EPA 1991a
Drinking water (1,4-DCB)	Purge and trap	GC/HECD; conf. on second col. or GC/MS	<0.01 μg/L for most VOCs	90	Method 502.1 EPA 1991a
Drinking water (1,2-DCB)	Purge and trap	GC/PID-HECD; conf. by GC/MS	0.03–0.05 μg/L (PID); 0.02–0.04 μg/L (HECD)	97–102 (PID); 98–100 (HECD)	Method 502.2 EPA 1991b
Drinking water (1,3-DCB)	Purge and trap	GC/PID-HECD; conf. by GC/MS	0.02 μg/L (PID); 0.02–0.07 μg/L (HECD)	97–104 (PID); 97–106 (HECD)	Method 502.2 EPA 1991b
Drinking water (1,4-DCB)	Purge and trap	GC/PID-HECD; conf. by GC/MS	0.01–0.03 μg/L (PID); 0.01–0.04 μg/L (HECD)	97–103 (PID); 97–98 (HECD)	Method 502.2 EPA 1991b
Drinking water (1,2-DCB)	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.02 μg/L	75–85	Method 503.1 EPA 1991c

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

Sample matrix (analyte)	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water (1,3-DCB)	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.006 μg/L	91	Method 503.1 EPA 1991c
Drinking water (1,4-DCB)	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.006 μg/L	91–107	Method 503.1 EPA 1991c
Drinking water	Purge and trap	cap. GC/MS	0.03–0.05 μg/L	93–97	Method 524.2 EPA 1992a
Drinking water	Purge and trap	cap. GC/MS	0.05–0.12 μg/L	87–100	Method 524.2 EPA 1992a
Drinking water	Purge and trap	cap. GC/MS	0.03–0.04 μg/L	93–103	Method 524.2 EPA 1992a
Waste water	Purge and trap	GC/HECD; conf. on second col. or GC/MS	0.15 μg/L	ND–208	Method 601 EPA 2002c
Waste water	Purge and trap	GC/HECD; conf. on second col. or GC/MS	0.32 μg/L	7–187	Method 601 EPA 2002c
Waste water	Purge and trap	GC/HECD; conf. on second col. or GC/MS	0.24 μg/L	42–143	Method 601 EPA 1984c; EPA 2002c
Waste water	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.4 μg/L	37–154	Method 602 EPA 2002d
Waste water	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.3 μg/L	50–141	Method 602 EPA 2002d
Waste water	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.3 μg/L	42–143	Method 602 EPA 1984f; EPA 2002d
Waste water	Solvent extraction; optional Florisil column clean-up	GC/ECD	1.14 μg/L	9–160	Method 612 EPA 2002b
Waste water	Solvent extraction; optional Florisil column clean-up	GC/ECD	1.19 μg/L	DL–150	Method 612 EPA 2002b
Waste water	Solvent extraction; optional Florisil column clean-up	GC/ECD	1.34 μg/L	13–137	Method 612 EPA 1984c; EPA 2002b
Waste water (1,2- and 1,4-DCB)	Purge and trap	GC/MS	No data	18–190	Method 624 EPA 1984d; EPA 2002a
Waste water (1,3-DCB)	Purge and trap	GC/MS	No data	59–156	Method 624 EPA 1984d; EPA 2002a
Waste water	Purge and trap	cap. GC/MS	0.031 μg/L	106	Method 6200B APHA 1998

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

Sample matrix (analyte)	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water	Purge and trap	cap. GC/MS	0.045 μg/L	108	Method 6200B APHA 1998
Waste water	Purge and trap	cap. GC/MS	0.033 μg/L	106	Method 6200B APHA 1998
Waste water/ Drinking water (1,2-DCB)	Purge and trap	cap GC/HECD, PID	0.023 μg/L (HECD); 0.031 μg/L (PID)	93 (HECD); 67 (PID)	Method 6200 APHA 1998
Waste water/ Drinking water (1,3-DCB)	Purge and trap	cap GC/HECD, PID	0.017 μg/L (HECD); 0.028 μg/L (PID)	95 (HECD); 70 (PID)	Method 6200 APHA 1998
Waste water/ Drinking water (1,4-DCB)	Purge and trap	cap GC/HECD, PID	0.059 μg/L (HECD); 0.061 μg/L (PID)	91 (HECD); 70 (PID)	Method 6200 APHA 1998
Drinking water (VOCs)	Purge and trap	GC	low μg/L	99	Method D 3871 ASTM 1994
Solid waste (VOCs)	Closed system purge and trap and extraction	GC/ECD, FID, MS	Not reported	Not reported	Method 5035 EPA 1996c
Solid waste (1,2-DCB)	Purge and trap, direct injection, headspace, or vacuum distillation	GC/HECD, PID	0.02 μg/L (HECD); 0.05 (PID)	100 (HECD); 102 (PID)	Method 8021B EPA 1996d
Solid waste (1,3-DCB)	Purge and trap, direct injection, headspace, or vacuum distillation	GC/HECD, PID	0.02 μg/L (HECD); 0.02 (PID)	106 (HECD); 104 (PID)	Method 8021B EPA 1996d
Solid waste (1,4-DCB)	Purge and trap, direct injection, headspace, or vacuum distillation	GC/HECD, PID	0.01 μg/L (HECD); 0.07 (PID)	98 (HECD); 103 (PID)	Method 8021B EPA 1996d
Solid waste (1,2-DCB)	Solvent extraction	Single or dual cap. GC/ECD	270 ng/L	102	Method 8121 EPA 1994l
Solid waste (1,3-DCB)	Solvent extraction	Single or dual cap. GC/ECD	250 ng/L	103	Method 8121 EPA 1994l
Solid waste (1,4-DCB)	Solvent extraction	Single or dual cap. GC/ECD	890 ng/L	104	Method 8121 EPA 1994l

[a]Estimated limit of detection

cap. = capillary; conf. = confirmation; col. = column; DL = detection limit; ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HECD = Hall electrolytic conductivity detector; MS = mass spectrometry; ND = not detected; PID = photoionization detector; VOC = volatile organic compound

(EPA 1988a), but performance data are unavailable. Passive sampling devices are also widely used, due in part to their ease of use and small size (Lewis et al. 1985).

For water, soil, or sediment samples, DCBs are purged from the sample with an inert gas such as helium or nitrogen, and then passed through the sorbent (EPA 1984a, 1984b, 1991a, 1991b, 1991c, 1992a, 1994a, 1994f). The analytes are thermally desorbed and analyzed by GC/HECD, GC/PID, GC/ECD, or GC/MS techniques. Detection limits for waste waters and solid wastes are in the low-ppb range, which is probably well below levels of health concern. Detection limits for drinking water samples are generally in the ppt range (0.006–0.05 μg/L) (EPA 1991a, 1991b, 1991c, 1992a).

Several physical parameters may interfere with analytical accuracy. High sampling flow rates and high temperature and humidity may cause decreased adsorption of DCB vapor on the solid sorbent (APHA 1995a). Interference by other VOCs with similar retention times may be resolved by using different GC column materials and temperatures or be using MS techniques.

The use of capillary columns rather than packed column GC has improved resolution and sensitivity and shortened the analysis time (Washall and Wampler 1988). However, more stringent sample clean-up procedures are required for capillary column GC (Oliver and Nicol 1982b). The development of methods using whole column cryotrapping (Pankow and Rosen 1988; Pankow et al. 1988) and cryogenic refocusing (Washall and Wampler 1988) provide even greater sensitivity and resolution for GC analysis.

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 dichlorobenzenes 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 dichlorobenzenes.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Exposure to DCBs may be evaluated by measuring the levels of these compounds in blood, breath, milk, and adipose tissue, and by measuring the level of 2,5-dichlorophenol, a metabolite of 1,4-DCB, or the levels of 2,3-dichlorophenol, 3,4-dichlorophenol, 3,4-dichlorocatechol, and 4,5-dichlorocatechol, metabolites of 1,2-DCB, in urine (Bristol et al. 1982; Erickson et al. 1980; Jan 1983; Kumagai and Matsunaga 1995, 1997; Langhorst and Nestrick 1979; Mage et al. 2004; Pellizzari et al. 1985). Sensitive analytical methods are available for measurements in blood. Development of methods with improved specificity and sensitivity for other tissues and breath would be valuable in identifying individuals with low-level exposure. Development of standardized procedures would permit comparison of data and facilitate the study of correlations between exposure and measured levels biological samples. Interlaboratory studies are also needed to provide better performance data for methods currently in use.

Effect. There are no known health effects such as elevated liver enzymes that are uniquely associated with exposure to DCBs. Therefore, the identification of specific health effects and the development of analytical methods to determine biomarkers of effect for DCBs would be useful.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Air is the environmental medium of most concern for human exposure to DCBs. Exposure from drinking water may also be of concern in some areas, such as near hazardous waste sites. Existing analytical methods can measure DCBs in these and other environmental media at background levels (EPA 1988a, 1984a, 1984b, 1991a, 1991b, 1991c, 1992a, 1994a, 1994f; NIOSH 1994). The accuracy and precision of the methods for water and wastes are well documented and MS provides adequate specificity. Performance data for measurements in ambient and indoor air would be helpful. Development of techniques to improve the accuracy and ease of sample preparation and transfer for these methods would also be helpful.

7.3.2 Ongoing Studies

No ongoing studies involving analytical techniques for DCBs were found in a search of the Federal Research in Progress database (FEDRIP 2005).

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8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines pertaining to dichlorobenzenes in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an MRL of 2 ppm for acute-duration inhalation exposure to 1,4-DCB. The acute inhalation MRL is based on a NOAEL of 15 ppm for irritant effects in humans exposed to 1,4-DCB in the workplace (Hollingsworth et al. 1956). An uncertainty factor of 10 for human variability was applied.

ATSDR has derived an MRL of 0.2 ppm for intermediate-duration inhalation exposure to 1,4-DCB. The intermediate inhalation MRL is based on benchmark dose analysis of liver weight increases in male rats exposed to 1,4-DCB vapors for 6 hours/day for 15 weeks (Tyl and Neeper-Bradley 1989). The resulting $BMCL_{1sd}$ of 92.45 ppm was duration-adjusted from intermittent to continuous exposure, converted to a human equivalent concentration (23 ppm), and divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.01 ppm for chronic-duration inhalation exposure to 1,4-DCB. The chronic inhalation MRL is based on benchmark dose analysis of incidences of nasal lesions in female rats exposed to 1,4-DCB vapors for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b). The resulting $BMCL_{10}$ of 9.51 ppm was duration-adjusted from intermittent to continuous exposure, converted to a human equivalent concentration (0.27 ppm), and divided by an uncertainty factor of 30 (3 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.7 mg/kg/day for acute-duration oral exposure to 1,2-DCB. The acute oral MRL is based on benchmark dose analysis of liver weight increases in female rats administered 1,2-DCB by daily oral gavage for 10 days (Robinson et al. 1991). The resulting $BMDL_{1sd}$ of 67.73 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.6 mg/kg/day for intermediate-duration oral exposure to 1,2-DCB. The intermediate oral MRL is based on benchmark dose analysis of liver weight increases in female rats administered 1,2-DCB by oral gavage on 5 days/week for 13 weeks (NTP 1985). The resulting $BMDL_{1sd}$ of 89.27 mg/kg/day was duration-adjusted from intermittent to daily exposure (63.76 mg/kg/day) and

divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.3 mg/kg/day for chronic-duration oral exposure to 1,2-DCB. The chronic oral MRL is based on benchmark dose analysis of incidences of kidney lesions in male mice administered 1,2-DCB by oral gavage on 5 days/week for 103 weeks (NTP 1985). The resulting $BMDL_{10}$ of 43.04 mg/kg/day was duration-adjusted from intermittent to daily exposure (30.74 mg/kg/day) and divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.4 mg/kg/day for acute-duration oral exposure to 1,3-DCB. The acute oral MRL is based on benchmark dose analysis of liver weight increases in female rats administered 1,3-DCB by oral gavage for 10 days (McCauley et al. 1995). The resulting $BMDL_{1sd}$ of 36.32 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.02 mg/kg/day for intermediate-duration oral exposure to 1,3-DCB. The intermediate oral MRL is based on benchmark dose analysis of incidences of pituitary lesions in male rats administered 1,3-DCB by daily oral gavage for 90 days (McCauley et al. 1995). The resulting $BMDL_{10}$ of 2.1 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.07 mg/kg/day for intermediate-duration oral exposure to 1,4-DCB. The intermediate oral MRL is based on benchmark dose analysis of serum alkaline phosphatase levels in female dogs administered 1,4-DCB by capsule on a presumed 5 days/week for 6 months (Naylor and Stout 1996). The resulting $BMDL_{1sd}$ of 9.97 mg/kg/day was duration-adjusted from intermittent to daily exposure (7 mg/kg/day) and divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

ATSDR has derived an MRL of 0.07 mg/kg/day for chronic-duration oral exposure to 1,4-DCB. The chronic oral MRL is based on benchmark dose analysis of serum alkaline phosphatase levels in female dogs administered 1,4-DCB by capsule on a presumed 5 days/week for 1 year (Naylor and Stout 1996). The resulting $BMDL_{1sd}$ of 10 mg/kg/day was duration-adjusted from intermittent to daily exposure

(7 mg/kg/day) and divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

EPA has verified an oral reference dose (RfD) of 0.09 mg/kg/day for 1,2-DCB based on a NOAEL of 85.7 mg/kg/day for kidney effects in rats and an uncertainty factor of 1,000 (IRIS 2005). EPA also verified an inhalation reference concentration (RfC) of 0.8 mg/m^3 (0.1 ppm) for 1,4-DCB based on a NOAEL of 75 mg/m^3 for liver effects in rats and an uncertainty factor of 100 (IRIS 2005).

EPA has determined that 1,2-DCB and 1,3-DCB are not classifiable as to human carcinogenicity and assigned them cancer weight-of-evidence classification Group D (IRIS 2005). IARC similarly determined that 1,2-DCB and 1,3-DCB are not classifiable as to carcinogenicity to humans (Group 3) (IARC 1999). IARC additionally determined that 1,4-DCB is possibly carcinogenic to humans (Group 2B) (IARC 1999). The Department of Health and Human Services (DHHS) concluded that 1,4-DCB is reasonably anticipated to be a human carcinogen (NTP 2005).

Table 8-1. Regulations and Guidelines Applicable to Dichlorobenzenes

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		
	1,2-Dichlorobenzene	Group 3[a]	IARC 1999
	1,3-Dichlorobenzene	Group 3[a]	
	1,4-Dichlorobenzene	Group 2B[b]	
WHO	Air quality guideline	No data	WHO 2000
	Drinking water guideline		
	1,2-Dichlorobenzene	1 mg/L[c]	WHO 2004
	1,3-Dichlorobenzene	Toxicological data are insufficient to permit derivation of health-based guideline value	
	1,4-Dichlorobenzene	0.3 mg/L[c]	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2003
	1,2-Dichlorobenzene	25 ppm	
	STEL	50 ppm	
	Carcinogenicity classification	A4[d]	
	1,4-Dichlorobenzene	10 ppm	
	Carcinogenicity classification	A3[e]	
EPA	Hazardous air pollutant		EPA 2004h 42USC7412
	1,4-Dichlorobenzene	Yes	
NIOSH	REL (10-hour TWA)		NIOSH 2004
	1,2-Dichlorobenzene (ceiling limit)	50 ppm	
	1,4-Dichlorobenzene	Carcinogen	
	IDLH		
	1,2-Dichlorobenzene	200 ppm	
	1,4-Dichlorobenzene	150 ppm	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2004c 29CFR1910.1000, Table Z-1
	1,2-Dichlorobenzene (ceiling limit)	50 ppm	
	1,4-Dichlorobenzene	75 ppm	
	PEL (8-hour TWA) for construction industry		OSHA 2004b 29CFR1926.55, Appendix A
	1,2-Dichlorobenzene (ceiling limit)	50 ppm	
	1,4-Dichlorobenzene	75 ppm	

Table 8-1. Regulations and Guidelines Applicable to Dichlorobenzenes

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	PEL (8-hour TWA) for shipyard industry		OSHA 2004a 29CFR1915.1000, Table Z
	1,2-Dichlorobenzene (ceiling limit)	50 ppm	
	1,4-Dichlorobenzene	75 ppm	
b. Water			
EPA	Designated as a hazardous substances pursuant to Section 311(b) of the Clean Water Act		EPA 2004m 40CFR116.4
	1,2-Dichlorobenzene	Yes	
	1,4-Dichlorobenzene	Yes	
	Drinking water standard		EPA 2004g 40CFR141.32
	1,2-Dichlorobenzene	0.6 mg/L	
	1,4-Dichlorobenzene	0.075 mg/L	
	Drinking water standards and health advisories		EPA 2004a
	1,2-Dichlorobenzene and 1,3-dichlorobenzene		
	1-Day HA for a 10-kg child	9 mg/L	
	10-Day HA for a 10-kg child	9 mg/L	
	DWEL	3 mg/L	
	Lifetime HA (70-kg adult)	0.6 mg/L	
	1,4-Dichlorobenzene		
	1-Day HA for a 10-kg child	11 mg/L	
	10-Day HA for a 10-kg child	11 mg/L	
	DWEL	4 mg/L	
	Lifetime HA (70-kg adult)	0.075 mg/L	
	MCL		EPA 2004f 40CFR141.61
	1,2-Dichlorobenzene	0.6 mg/L	
	1,4-Dichlorobenzene	0.075 mg/L	
	MCLG		EPA 2004d 40CFR141.50
	1,2-Dichlorobenzene	0.6 mg/L	
	1,4-Dichlorobenzene	0.075 mg/L	
FDA	Bottled water		FDA 2003 21CFR165.110
	1,2-Dichlorobenzene	0.6 mg/L	
	1,4-Dichlorobenzene	0.075 mg/L	
c. Food			
	No data		
d. Other			
EPA	Carcinogenicity classification		IRIS 2004
	1,2-Dichlorobenzene	Group D[f]	
	1,3-Dichlorobenzene	Group D[f]	
	1,4-Dichlorobenzene	No data	
	RfC		

Table 8-1. Regulations and Guidelines Applicable to Dichlorobenzenes

Agency	Description	Information	Reference
	1,2-Dichlorobenzene	No data	
NATIONAL *(cont.)*			
	1,3-Dichlorobenzene	No data	
	1,4-Dichlorobenzene	$8x10^{-1}$ mg/m^3	
EPA	RfD		
	1,2-Dichlorobenzene	$9x10^{-2}$ mg/kg/day	IRIS 2004
	1,3-Dichlorobenzene	No data	
	1,4-Dichlorobenzene	No data	
	Community right-to-know; toxic chemical release reporting; effective date		EPA 2004j 40CFR372.65
	1,2-Dichlorobenzene	01/01/1987	
	1,3-Dichlorobenzene	01/01/1987	
	1,4-Dichlorobenzene	01/01/1987	
	Hazardous waste identification		
	1,2-Dichlorobenzene	U070	EPA 2004c 40CFR261, Appendix VIII
	1,3-Dichlorobenzene	U071	
	1,4-Dichlorobenzene	U072	
	Chemical information rules; manufacturers reporting period for 1,2-dichlorobenzene and 1,4-dichloro-benzene		EPA 2004k 40CFR712.30
	Effective date	08/04/1995	
	Sunset date	10/03/1995	
	Superfund; reportable quantity		
	1,2-Dichlorobenzene[g]	100 pounds	EPA 2004b 40CFR302.4
	1,3-Dichlorobenzene[h]	100 pounds	
	1,4-Dichlorobenzene[i]	100 pounds	
NTP	Carcinogenicity classification		
	1,2-Dichlorobenzene	No data	
	1,3-Dichlorobenzene	No data	NTP 2005
	1,4-Dichlorobenzene	Reasonably anticipated to be a human carcinogen	
STATE			
a. Air			
	No data		
b. Water			
	Drinking water standards and guidelines		HSDB 2005
Arizona	1,2-Dichlorobenzene	620 µg/L	
	1,3-Dichlorobenzene	620 µg/L	
	1,4-Dichlorobenzene	75 µg/L	
California	1,3-Dichlorobenzene	130 µg/L	
	1,4-Dichlorobenzene	5 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Dichlorobenzenes

Agency	Description	Information	Reference
Florida	1,3-Dichlorobenzene	10 μg/L	
STATE *(cont.)*			
Maine	1,2-Dichlorobenzene	63 μg/L	
	1,4-Dichlorobenzene	21 μg/L	
Massachusetts	1,4-Dichlorobenzene	5 μg/L	
Minnesota	1,2-Dichlorobenzene	600 μg/L	
	1,4-Dichlorobenzene	10 μg/L	
New Jersey	1,2-Dichlorobenzene	600 μg/L	
	1,3-Dichlorobenzene	600 μg/L	
Wisconsin	1,3-Dichlorobenzene	1,250 μg/L	
c. Food			
	No data		
d. Other			
	No data		

[a]Group 3: Not classifiable as to its carcinogenicity to humans.
[b]Group 2B: Possibly carcinogenic to humans.
[c]Concentrations of the substance at or below the health-based guideline value may affect the appearance, taste or odor of the water, leading to consumer complaints.
[d]Group A4: Not classifiable as a human carcinogen.
[e]Group A3: Confirmed animal carcinogen with unknown relevance to humans.
[f]Group D: Not classifiable as to human carcinogenicity.
[g]Designated as a hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act, Section 307(a) of the Clean Water Act, and Section 3001 of RCRA.
[h]Designated as a hazardous substance pursuant to Section 307(a) of the Clean Water Act and Section 3001 of RCRA.
[i]Designated as a hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act, Section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HA = health advisory; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Codes; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 1
Species: Human

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

Reference: Hollingsworth RL, Rowe VK, Oyen F, et al. 1956. Toxicity of paradichlorobenzene: Determinations on experimental animals and human subjects. AMA Arch Ind Health 14:138-147.

Experimental design: Periodic occupational health examinations were conducted on 58 men who had worked in unspecified industrial operations involving the handling of 1,4-DCB, generally for 8 hours/day and 5 days/week, continually or intermittently for periods of 8 months to 25 years (average 4.75 years). Effects of different workplace exposure levels on eye and nose irritation were summarized. The medical evaluations included careful examination of the eyes, blood cell counts (RBC, WBC, and differential), hemoglobin, hematocrit, mean corpuscular volume, blood urea nitrogen, sedimentation rate, and urinalysis.

Effects noted in study and corresponding doses: Observations in the workers provide information relevant to acute exposures. The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. The odor and irritation properties were considered to be fairly good acute warning properties and were expected to prevent excessive exposures, although the industrial experience indicated that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor. No cataracts or any other lens changes in the eyes, or effects on the clinical indices were attributable to exposure.

Dose and end point used for MRL derivation:

[15] NOAEL [] LOAEL

As discussed above, eye and nose irritation are critical effects of acute inhalation exposure to 1,4-DCB in humans. Because odor detection is a warning property expected to prevent irritation caused by 1,4-DCB, the highest level at which an odor was detected that was simultaneously without irritant effects, 30 ppm, was designated a minimal LOAEL for irritation for the purposes of derivation of the MRL; the 15 ppm level was therefore designated a NOAEL for irritant effects.

Uncertainty Factors used in MRL derivation:

[X] 10 for human variability

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

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

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: A limited amount of information is available on the toxicity of inhaled 1,4-DCB in humans. Case reports of people who inhaled 1,4-DCB provide indications that the liver and nervous system are systemic targets of inhalation toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-DCB was the only factor associated with the effects (Cotter 1953; Miyai et al. 1988; Reygagne et al. 1992).

Information on effects of acute-duration inhalation exposure to 1,4-DCB in animals is available from short-term systemic toxicity studies in rats and guinea pigs (Hollingsworth et al. 1956), a male reproduction study rats (Anderson and Hodge 1976), and developmental toxicity studies in rats and rabbits (Hayes et al. 1985; Hodge et al. 1977). In the systemic toxicity study, five rats of each sex and five guinea pigs of each sex were exposed to 175 ppm of 1,4-DCB for 7 hours/day, 5 days/week for 16 days (Hollingsworth et al. 1956). Mild histological effects of interstitial edema, congestion, and alveolar hemorrhage were observed in the lungs of male rats and female guinea pigs. The experimental design and report of this study have a number of deficiencies, such that reported observations provide only qualitative evidence of exposure-related respiratory effects. In the reproduction study (a dominant lethal test), a NOAEL of 450 ppm was identified for reproductive performance in male mice that were exposed for 6 hours/day for 5 days prior to weekly mating with unexposed females for 8 weeks (Anderson and Hodge 1976). No maternal or developmental toxicity occurred in rats that were exposed to 75–500 ppm for 6 hours/day on days 6–15 of gestation (Hodge et al. 1977), indicating that the highest NOAEL for reproductive effects in rats is 500 ppm. A developmental study in which rabbits were exposed to 100–800 ppm for 6 hours/day on gestation days 6–18 found evidence of fetotoxicity (a minor variation of the circulatory system) only at 800 ppm, which was also maternally toxic as shown by body weight loss early in gestation (Hayes et al. 1985), indicating that 800 ppm is a LOAEL for maternal and developmental effects in rabbits.

The lung appears to be a target of concern for inhaled 1,4-DCB in rats and guinea pigs exposed to 173 ppm (Hollingsworth et al. 1956), because the only effects observed in the reproductive and developmental studies were indications of maternal and fetotoxicity in rabbits at a much higher levels of 800 ppm (Hayes et al. 1985). Support for the respiratory tract as a sensitive target for 1,4-DCB inhalation in animals is provided by the induction of nasal lesions in rats intermittently exposed to levels as low as 75 ppm for 104 weeks in the study used to derive the chronic inhalation MRL for 1,4-DCB (Japan Bioassay Research Center 1995). Additionally, the animal data are consistent with the human experience, indicating that occupational exposure to 1,4-DCB causes painful nose and eye irritation in the range of 50–160 ppm (Hollingsworth et al. 1956).

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 14
Species: Rat

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

References: Aiso A, Arito H, Nishizawa T, et al. 2005a. Thirteen-week inhalation toxicity of *p*-dichlorobenzene in mice and rats. J Occup Health 47:249-260.

Tyl RW, Neeper-Bradley TL. 1989. Paradichlorobenzene: Two generation reproductive study of inhaled paradichlorobenzene in Sprague-Dawley (CD) rats. Laboratory Project 86-81-90605. Washington, DC: Chemical Manufacturers Association, Chlorobenzene Producers Association.

Experimental design and effects noted (Aiso et al. 2005a): This is a systemic toxicity study in which groups of 10 male and 10 female F344 rats and 10 male and 10 female BDF_1 mice were chamber-exposed to 1,4-DCB vapor (>99.9% pure) at target concentrations of 0, 25, 55, 120, 270, or 600 ppm for 6 hours/day, 5 days/week for 13 weeks. Deviations in mean observed concentrations from the target concentrations were <9.6%. End points evaluated during the study included clinical signs (daily) and body weight and food consumption (weekly). End points evaluated at the end of the 13-week exposure period included hematology (RBC, Hb, Hct, MCV, MCH), blood biochemistry (total protein, albumin, total cholesterol, triglyceride, phospholipid, AST, ALT, AP, BUN, creatine), organ weights, and histopathology. The histological examinations were comprehensive and included the nasal cavity, in accordance with OECD test guidelines for a 90-day inhalation study (Aiso 2005a; OECD 1981).

There were no exposure-related effects on survival, clinical signs, or body weight gain in the rats. Hematological changes suggestive of microcytic anemia occurred in male rats, including significantly decreased RBC count and hemoglobin concentration at ≥120 ppm, hematocrit at ≥270 ppm, and MCV and MCH at 600 ppm. Serum biochemical changes included significant increases in total protein in both sexes at 600 ppm, albumin in females at ≥270 ppm and males at 600 ppm, and total cholesterol and phospholipid in males at ≥270 ppm and females at 600 ppm, and significant decreases in triglycerides in males at 600 ppm, AST in both sexes at 600 ppm, and ALT and AP in males at ≥270 ppm. Organ weight changes included >10% increases in absolute and relative weights of liver in males at ≥270 ppm and females at 600 ppm, kidneys in males at ≥270 ppm, and spleen in males at 600 ppm. Histological effects included significantly increased incidences of liver centrilobular hepatocellular hypertrophy in male rats at 600 ppm (incidences in the control to high dose groups were 0/10, 0/10, 0/10, 0/10, 3/10, and 10/10), and kidney lesions indicative of $\alpha_{2\mu}$-globulin nephropathy (hyaline droplets, granular casts, tubular cell necrosis, cytoplasmic basophila, and papillary mineralization) in male rats at ≥270 ppm. There were no histopathological changes in hematopoietic tissues (e.g., increased extramedullary hematopoiesis or hemosiderosis in the spleen), leading the investigators to suggest the possibility that the anemia in the male rats was secondary to $\alpha_{2\mu}$-globulin nephropathy-related effects on erythropoietin synthesis in the renal tubules.

There were no exposure-related effects on survival, clinical signs, or body weight gain in the mice. Organ weight changes in the mice included >10% increases in liver weight in males at ≥270 ppm (relative) and

600 ppm (absolute) and females at 600 ppm (absolute and relative); relative liver weights were 9.7, 9.7, 10.1, 23.9, and 62.6% higher than controls in the low- to high-dose males. There were no significant hematological changes in either sex. Serum ALT levels were significantly increased in males at ≥270 ppm (18.2, 9.1, 18.2, 54.5, and 164% higher than controls in the low- to high-dose groups). Other serum biochemical changes included significant increases in ALT in females at 600 ppm, AST in males at 600 ppm, and total cholesterol and total protein in both sexes at 600 ppm. Histological examinations showed significantly ($p \leq 0.01$) increased incidences of centrilobular hepatocellular hypertrophy at in male mice at ≥270 ppm and female mice at 600 ppm; incidences in the control to high dose groups were 0/10, 0/10, 0/10, 0/10, 10/10, and 10/10 in the males and 0/10, 0/10, 0/10, 0/10, 0/10, and 10/10 in the females. Affected hepatocytes were characterized by cell enlargement, varying nuclear size and shape, and coarse chromatin and inclusion bodies in the nucleus; the severity of these lesions was rated as slight at 270 ppm (males) and moderate at 600 ppm (both sexes). The moderate hepatocellular hypertrophy in the 600 ppm male mice was accompanied by single cell necrosis (1/10) and focal liver necrosis (2/10).

The lowest effect level is 270 ppm based on the kidney and hematological effects in male rats and liver effects in rats and mice. The kidney and hematological effects are consistent with $\alpha_{2\mu}$-globulin nephropathy, which is specific to male rats and not relevant to humans. The mice were more sensitive to the liver effects of 1,4-DCB than the rats because the only hepatic change in the 270 ppm rats was increased liver weight, whereas hepatocellular hypertrophy and increased serum ALT occurred in addition to increased liver weight in the 270 ppm mice. Additionally, at the next highest tested level of 600 ppm, the mice had nuclear changes and evidence of necrosis in the hypertrophic hepatocytes, and increased serum AST as well as ALT, whereas none of these indicators of hepatocellular damage occurred in the rats. Based on increased relative liver weight (>10%) in both species and histological and serum ALT changes in the mice, this study identified a NOAEL of 120 ppm and a LOAEL of 270 ppm for hepatic effects. The identification of the liver as a critical target of 1,4-DCB is supported by findings of increased liver weight and serum liver enzymes, as well as histopathologic liver lesions in dogs administered 1,4-DCB orally for up to 1 year (Naylor and Stout 1996).

Experimental design and effects noted (Tyl and Neeper-Bradley 1989): This is a two-generation study in which groups of 28 Sprague-Dawley rats of each sex were exposed to actual mean 1,4-DCB concentrations of 0, 66, 211, and 538 ppm for 6 hours/day, 7 days/week. Additional groups of 10 females were similarly exposed for 10 weeks in a satellite study. The animals in the main study were paired within groups for a 3-week mating period to produce the F_1 generation. Main study males that did not successfully mate in the first 10 days of the mating period were paired with the satellite females for 10 days. Main study females that did not successfully mate during the first 10 days of the mating period were paired with proven males for the remaining 11 days of the mating period. Exposures of the main study F_0 females were continued throughout the mating period and the first 19 days of gestation, discontinued from gestation day 20 through postnatal day 4, and then resumed until sacrifice at weaning on postnatal day 28. Exposures of the satellite F_0 females were continued through mating until sacrifice on gestation day 15. Exposures of the F_0 males continued until sacrificed at the end of the study and satellite mating periods (F_0 males were exposed for a total of 15 weeks). Groups of 28 F_1 weanlings/sex and satellite groups of 10 F_1 female weanlings were exposed for 11 weeks and mated as described above to produce the F_2 generation. Additionally, 20 F_1 weanlings/sex from the control and high exposure groups served as recovery animals that were observed without exposure for 5 weeks prior to sacrifice. Complete necropsies were performed on all F_0 and F_1 adult (parental) animals, F_1 recovery animals, F_1 weanlings not used in the rest of the study, and F_2 weanlings, and histology was evaluated in the F_0 and F_1 parental animals. Histological examinations were conducted on the liver and kidneys in all groups and on selected other tissues (pituitary, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, prostate, and tissues with gross lesions) in the control and high exposure groups. The kidney evaluation included examination for the presence of $\alpha 2_{\mu}$ droplets. Additional end points evaluated in the parental generations included clinical observations, mortality, body weight, and food consumption. Mating and

fertility indices were determined for F_0 and F_1 males and females, and gestational, live birth, postnatal survival (4-, 7-, 14-, 21-, and 28-day), and lactation indices were determined for the F_1 and F_2 litters.

There were no effects on reproductive parameters in either generation, although systemic toxicity occurred at all dose levels in F_0 and F_1 adult rats. Hyaline droplet nephropathy was found in F_0 and F_1 adult males at ≥66 ppm. Manifestations of this male rat-specific renal syndrome included $\alpha_{2\mu}$-globulin accumulation and increased kidney weights at ≥66 ppm, and other characteristic histological changes at 538 ppm. Body weights and weight gain were significantly reduced in F_0 and F_1 adult males and F_1 adult females during the pre-breed exposure periods at 538 ppm. Absolute liver weights were increased in F_0 males by 6, 16, and 38% in the 66, 211, and 538 ppm groups, respectively; the differences were statistically significantly different from control in the 211 and 538 ppm groups. In F_0 females, absolute liver weights were increased by 9 and 31% at 211 and 538 ppm, respectively, but statistical significance was achieved only at 538 ppm. Similar changes were seen in relative liver weights of the F_0 generation, with respective increases of 5, 14, and 52% in the 66, 211, and 538 ppm males and 4, 9, and 31% in the 66, 211, and 538 ppm females; all groups of treated males, and the 211 and 538 ppm female groups, were statistically significantly different from controls. Relative liver weights were also significantly increased in F_1 adult males at ≥211 ppm and F_1 adult females at 538 ppm. Hepatocellular hypertrophy was observed in the livers of F_0 and F_1 males and females at 538 ppm; no hepatic histological changes were induced at the lower exposure concentrations. Other effects also occurred in the F_0 and F_1 males and females at 538 ppm, indicating that there was a consistent pattern of adult toxicity at the high exposure level, including reduced food consumption and increased incidences of clinical signs (e.g., tremors, unkempt appearance, urine stains, salivation, and nasal and ocular discharges); these effects only sporadically occurred at 211 ppm. Other effects at 538 ppm included reduced gestational and lactational body weight gain, and postnatal toxicity, as evidenced by increased number of stillborn pups, reduced pup body weights, and reduced postnatal survival in F_1 and/or F_2 litters. This study identified a (1) a NOAEL of 66 ppm and LOAEL of 211 ppm for increased (>10% above controls) relative liver weight in adult rats, and (2) a serious LOAEL of 538 ppm for systemic toxicity (central nervous system and other clinical signs) in adult rats and developmental toxicity (increased stillbirths and perinatal mortality) in their offspring. The identification of increased liver weight as a critical effect of 1,4-DCB toxicity is supported by findings of increased liver weight and serum liver enzyme levels and histopathologic liver lesions following repeated oral exposure (Naylor and Stout 1996).

<u>Dose and end point used for MRL derivation</u>:

[ ] NOAEL [ ] LOAEL [X] BMCL

As discussed below, a $BMCL_{1sd}$ of 92.45 ppm for increased liver weight in rats was used as the point of departure for the MRL.

Benchmark dose (BMD) analysis was conducted using the Tyl and Neeper-Bradley (1989) data for relative liver weight in adult male rats (Table A-1) and the Aiso et al. (2005a) serum ALT data in male rats (Table A-2). A benchmark response (BMR) of 1 standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. BMD analysis of the relative liver weight data from the Aiso et al. (2005a) study is precluded by insufficient information (standard deviations were not reported). Incidences of hepatocellular hypertrophy in the male mice of the Aiso et al. (2005a) study were not subjected to BMD analysis because the response was observed in 0% of control, 25, 55, and 120 ppm animals and in 100% of the 270 and 600 ppm animals. The F_1 and F_2 postnatal survival data (Tyl and Neeper-Bradley 1989) were not subjected to BMD analysis because the 211 ppm exposure level represents a NOAEL and the next higher exposure level (538 ppm) represents a frank effect level (FEL) for 4-day survival (12.6 and 28.1% reductions in 4-day survival of F_1 and F_2 pups, respectively) and clinical signs in F_0 males and females.

Table A-1. Relative Liver Weight Data for F_0 Male Rats Exposed to 1,4-Dichlorobenzene Vapors 6 Hours/Day for 15 Weeks

	Mean measured exposure concentration (ppm)			
	0	66	211	538
Group size	27	28	28	28
Relative liver weight (%)	3.465±0.2328[a]	3.631±0.2080[b]	3.945±0.2592[c]	5.271±0.2474[c]

[a]Mean ± standard deviation
[b]Significantly different (p<0.05) from control group
[c]Significantly different (p<0.01) from control group

Source: Tyl and Neeper-Bradley 1989

Table A-2. Serum ALT Data for Male Rats Exposed to1,4-Dichlorobenzene Vapors 6 Hours/Day, 5 Days/Week for 13 Weeks

	Mean measured exposure concentration (ppm)					
	0	25	55	120	270	600
Group size	10	10	10	10	10	10
Serum ALT (IU/L)[a]	11±2	13±8	12±4	13±4	17±3[b]	29±6[c]

[a]Mean ± standard deviation
[b]Significantly different (p<0.05) from control group
[c]Significantly different (p<0.01) from control group

Source: Aiso et al. 2005a

All appropriate continuous-variable (linear, polynomial, power) models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the serum ALT data from the male rats of the Aiso et al. (2005a) study (the Hill model was excluded due to an insufficient number of exposure groups). An assumption of constant variance resulted in a p-value <0.0005 for the test of constant variance and a non-homogeneous variance assumption was suggested. However, the assumption of non-homogeneous variance resulted in inadequately modeled variance (p-value <0.0005) and BMD analysis of the serum ALT data from the male rats of the Aiso et al. (2005a) study was considered an inadequate method for selecting a point of departure for deriving an intermediate-duration inhalation MRL for 1,4-DCB.

Available continuous-variable models were also fit to the Tyl and Neeper-Bradley (1989) data for changes in liver weight. A BMR of 1 standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. The simplest model (linear) for continuous data was initially fit to the data; constant variance was selected (Table A-3). The model output indicated that constant variance was appropriate, but inadequate model mean fit was obtained (p-value <0.01). The more complex (polynomial, power, Hill) models were also fit to the liver weight data. The Hill model provided inadequate mean fit due to an insufficient number of dose groups (4, including controls), which resulted in insufficient (0) degrees of freedom. The 2-degree polynomial provided adequate mean fit and the power model provided marginally adequate mean fit as indicated by the p-values for mean fit (Table A-3). The 2-degree polynomial model was the best fitting model (the adequate model with the lowest Akaike's Information Criteria [AIC]), predicting a BMC_{1sd} and $BMCL_{1sd}$

(lower 95% confidence limit on the BMC_{1sd}) of 119.91 and 92.45 ppm, respectively (Table A-3). A plot of observed and predicted relative liver weight from the 2-degree polynomial model is shown in Figure A-1.

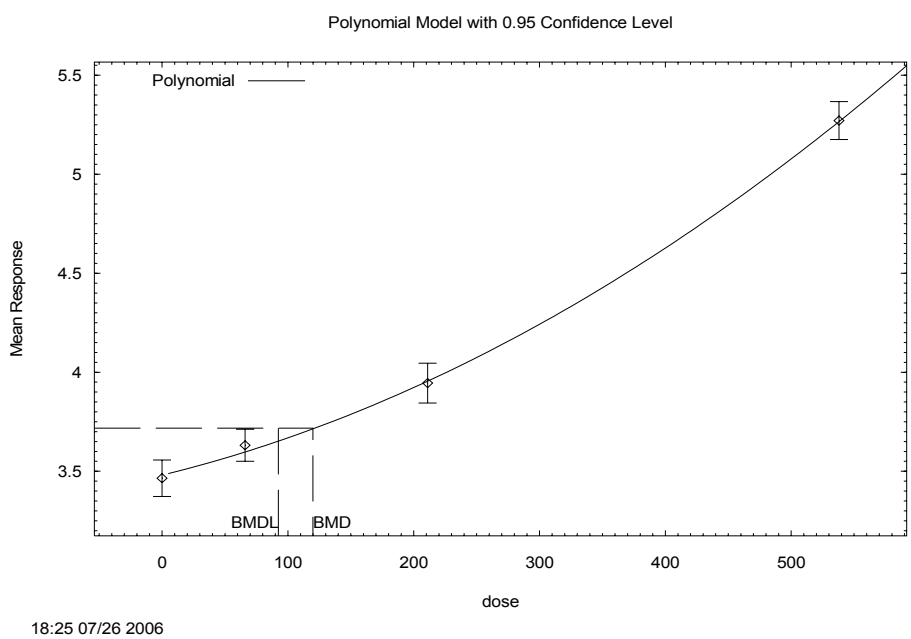
Table A-3. Model Predictions for Relative Liver Weight in F_0 Male Rats Exposed to 1,4-Dichlorobenzene Vapors 6 Hours/Day for 15 Weeks

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMC_{1sd} (ppm)	$BMCL_{1sd}$ (ppm)
Linear[b, c]	0.6877	0.00026	NA	NA	NA
2-Degree polynomial[b,c]	0.6877	0.3926	-205.3345	119.907	92.4533
Power[b]	0.9241	0.09954	-202.3525	129.587	100.477

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative

BMC_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation from the control mean; $BMCL_{1sd}$ = lower confidence limit (95%) on the BMC_{1sd}; NA = not applicable because model failed a goodness-of-fit test

Figure A-1. Observed Liver Weights in Adult Male Rats Exposed to 1,4-Dichlorobenzene for 15 Weeks and Predicted Relative Liver Weights by the 2-Degree Polynomial Model*



*BMD = BMC; BMDL=BMCL; BMC and BMCL (in ppm) are associated with a 1 standard deviation from the control mean.

The $BMCL_{1sd}$ of 92.45 ppm was duration-adjusted to 23 ppm, converted to a human equivalent concentration (HEC) of 23 ppm, and divided by an uncertainty factor of 100 to derive an MRL of 0.2 ppm.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Although the rat BMCL was adjusted to a HEC (see below), an uncertainty factor of 10 for extrapolation from animals to humans was still applied, because the HEC calculation was based on an assumption of equivalent blood-gas partition coefficients, and not on actual data.

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: 1,4-DCB exhibited the effects outside of the respiratory tract and consequently is treated as a category 3 gas for purposes of calculating the MRL. The HEC for extrarespiratory effects produced by a category 3 gas is calculated by multiplying the duration-adjusted $BMCL_{1sd}$ ($BMCL_{1sd\ ADJ}$, see below) by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994k). $H_{b/g}$ values were not available for 1,4-DCB in rats and humans. Using a default value of 1 for the ratio of partition coefficients, the $BMCL_{1sd\ HEC}$ becomes 23 ppm:

$$BMCL_{1sd\ HEC} = (BMCL_{1sd\ ADJ}) \times [(H_{b/g})_{RAT} / (H_{b/g})_{HUMAN}],$$
$$= 23 \text{ ppm} \times [1] = 23 \text{ ppm}$$

Was a conversion used from intermittent to continuous exposure? The $BMCL_{1sd}$ of 92 ppm was duration-adjusted for intermittent exposure, as follows (EPA 1994k):

$$BMCL_{1sd\ ADJ} = (BMCL_{1sd}) \text{ (hours/24 hours) (days/7 days)}$$
$$= (92.45 \text{ ppm}) \text{ (6 hours/24 hours) (7 days/7 days)}$$
$$= 23 \text{ ppm}$$

Other additional studies or pertinent information that lend support to this MRL: Supporting information on hepatic effects of intermediate-duration inhalation exposure to 1,4-DCB are available from a multispecies subchronic toxicity study in which rats, mice, guinea pigs, rabbits, and monkeys were exposed to 96 or 158 ppm for 7 hours/day, 5 days/week for 5–7 months (Hollingsworth et al. 1956). Some of these animals were also similarly exposed to 341 ppm for 6 months (rats and guinea pigs) or 798 ppm for 23–69 exposures (rats, guinea pigs, and rabbits). The experiments with rabbits and monkeys exposed to levels of 96 or 158 ppm are limited by small numbers of animals (1–2/group). Hepatic effects included increased relative liver weight and slight histological alterations in rats at 158 ppm (not observed at 96 ppm), and more severe histopathology (e.g., cloudy swelling and necrosis) in guinea pigs at 341 ppm, and in rats, guinea pigs, and rabbits at 798 ppm. Other findings in the animals exposed to 798 ppm included eye irritation and frank signs of neurotoxicity (e.g., marked tremors). The hepatic histological changes observed in rats at 158 ppm (cloudy swelling, congestion, or granular degeneration) were considered of questionable significance and were not reported at 358 ppm, indicating that neither 158 nor 358 ppm is a reliable LOAEL for liver pathology in rats in this study. The hepatic histological effects observed in the guinea pigs at 341 ppm appear have been more severe (fatty degeneration, focal necrosis, slight cirrhosis) than in rats, but only occurred in some of the animals (number not reported). Although this information suggests that 341 ppm is a LOAEL for liver histopathology in guinea pigs, confidence in this effect level is low due to imprecise and brief qualitative reporting of the results (a

general limitation of the study). The 798 ppm exposure concentration is a reliable LOAEL because this level clearly caused both liver histopathology (e.g., cloudy swelling and central necrosis) and overt signs of toxicity (e.g., marked tremors, eye irritation, and unconsciousness) in all three species.

A chronic inhalation study was conducted in which rats and mice were exposed to 1,4-DCB in target concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b). Effects in the rats included nasal lesions at ≥75 ppm and increased liver weight at 300 ppm, and effects in the mice included increased liver weight and hepatocellular hypertrophy at 300 ppm. The 75 ppm NOAEL and 300 ppm LOAEL for liver effects in the chronic study are consistent with the 120 ppm NOAEL and 211 ppm LOAEL for liver effects in the intermediate-duration studies (Aiso et al. 2005a; Tyl and Neeper-Bradley 1989). The 75 ppm LOAEL for nasal lesions in rats indicates that these tissues are more sensitive than the liver following chronic exposure, and the nasal lesions were used as the basis for the chronic inhalation MRL for 1,4-DCB. Because nasal lesions were not found in the 13-week study, it appears that the lesions are late-developing effects of chronic exposure. The lack of nasal lesions in the 13-week study therefore indicates that these are not critical effects of intermediate-duration exposure.

The NOAEL/LOAEL approach to MRL derivation results in the same MRL as the 0.2 ppm value derived using the BMD approach. The 13-week study (Aiso et al. 2005a) and two-generation study (Tyl and Neeper-Bradley 1989) are consistent in identifying the liver as the most sensitive target of intermediate duration inhalation of 1,4-DCB and showing that hepatic effects increased in severity with increasing level of exposure. The 13-week study (Aiso et al. 2005a) identified a hepatic NOAEL of 120 ppm and a LOAEL of 270 ppm in rats (increased liver weight) and mice (increased liver weight, hepatocellular hypertrophy, and serum ALT). The two-generation study identified a hepatic NOAEL of 66 ppm and a LOAEL of 211 ppm in rats (increased liver weight). The 120 ppm NOAEL is the highest hepatic NOAEL below the lowest hepatic LOAEL of 211 ppm, indicating that it is an appropriate basis for MRL derivation using the NOAEL/LOAEL approach. Using the NOAEL of 120 ppm for liver effects in male mice (the more sensitive species and sex), the NOAEL was duration-adjusted for the intermittent experimental exposure, as follows:

$$\begin{aligned} NOAEL_{ADJ} &= (NOAEL)\ (hours/24\ hours)\ (days/7\ days) \\ &= (120\ ppm)\ (6/24)\ (5/7) \\ &= 21.4\ ppm \end{aligned}$$

1,4-DCB exhibited the effects outside of the respiratory tract and consequently is treated as a category 3 gas for purposes of calculating the human equivalent concentration (HEC). The HEC for extra respiratory effects produced by a category 3 gas is calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994k). $H_{b/g}$ values were not available for 1,4-DCB in rats, mice and humans. Using a default value of 1 for the ratio of partition coefficients, the $NOAEL_{HEC}$ is 21.4 ppm, calculated as follows:

$$\begin{aligned} NOAEL_{HEC} &= (NOAEL_{ADJ}) \times [(H_{b/g})_{MOUSE} / (H_{b/g})_{HUMAN}], \\ &= 21.4.\ ppm \times [1] = 21.4\ ppm \end{aligned}$$

The $NOAEL_{HEC}$ was divided by the uncertainty factor of 100 to derive an MRL of 0.2 ppm.

<u>Agency Contact (Chemical Manager)</u>: Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 32
Species: Rat

Minimal Risk Level: [ ] mg/kg/day [0.01] ppm

References: Aiso S, Takeuchi T, Arito H, et al. 2005b. Carcinogenicity and chronic toxicity in mice and rats exposed by inhalation to *para*-dichlorobenzene for two years. J Vet Med Sci 67(10):1019-1029.

Japan Bioassay Research Center. 1995. Toxicology and carcinogenesis studies of p-dichlorobenzene in 344/DuCrj rats and Crj:BDF1 mice. Two-year inhalation studies. Japan Industrial Safety and Health Association. Study carried under contract with the Ministry of Labour of Japan.

Experimental design: Groups of 50 male and female F344/DuCrj rats and 50 male and female Crj:BDF_1 mice were exposed to 1,4-DCB in target concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks. Study end points included clinical signs and mortality, body weight (weekly for the first 13 weeks, and subsequently every 4 weeks), and hematology, blood biochemistry, and urinalysis indices (evaluated at end of study). Selected organ weight measurements (liver, kidneys, heart, lungs, spleen, adrenal, brain, testis, ovary) and comprehensive gross pathology and histology evaluations were performed on all animals at the end of the study or at time of unscheduled death. No interim pathology examinations were performed.

Effects noted in study and corresponding doses: For the rats, the actual mean chamber concentrations were 0, 19.8, 74.8, or 298.4 ppm over the duration of the study. The number of rats surviving to scheduled termination was significantly ($p<0.05$) reduced at 300 ppm in males. Survival in the male rats was noticeably lower than controls beginning at approximately study week 80, and overall survival at 0, 20, 75, and 300 ppm was 66% (33/50), 68% (34/50), 58% (29/50), and 36% (18/50), respectively. There were no exposure-related decreases in survival in the female rats, or effects on growth or food consumption in either sex. Changes in various hematological and blood biochemical indices (mean cell volume, total cholesterol, phospholipids, blood urea nitrogen, creatinine, and calcium in males; total protein, total bilirubin, blood urea nitrogen, and potassium in females) occurred at 300 ppm (Japan Bioassay Research Center 1995), but a lack of both numerical data and statistical analysis precludes interpretations of significance for these end points. Absolute and relative liver weights in both sexes and kidney weights in males were significantly increased at 300 ppm. Additional findings included histopathological changes in the nasal epithelia and kidneys. The nasal lesions mainly included increased incidences of eosinophilic changes (globules) in the olfactory epithelium (moderate or greater severity) in males at 300 ppm and females at ≥75 ppm. Incidences of this lesion at 0, 20, 75, and 300 ppm were 1/50, 2/50, 2/50, and 7/50 in males, and 27/50, 29/50, 39/50, and 47/50 in females. The increases were statistically significant ($p\leq0.05$, Fisher's Exact Test performed by ATSDR) at ≥75 ppm in females and 300 ppm in males, and there was a trend of increasing response with increasing dose in both sexes (Cochran-Armitage test, performed by ATSDR). Other nasal lesions that were significantly increased at 300 ppm were eosinophilic globules in the respiratory epithelium (11/50, 10/50, 14/50, 38/50) and respiratory metaplasia in the nasal gland (5/50, 4/50, 4/50, 33/50) in females at 300 ppm. Kidney lesions were increased only in male rats at 300 ppm and included significantly increased incidences of

mineralization of the renal papilla (0/50, 1/50, 0/50, 41/50) and in hyperplasia of the urothelium (7/50, 8/50, 13/50, 32/50).

For the mice, the actual mean chamber concentrations were 0, 19.9, 74.8, or 298.3 ppm over the duration of the study. Survival was significantly reduced in male mice at 300 ppm (due to an increase in liver tumor deaths), but comparable to controls in the females. Terminal body weight was significantly reduced at 300 ppm in males (11.5% less than controls, beginning at study week 80). Changes in various hematological and blood biochemical indices (total cholesterol, SGOT, SGPT, LDH, and AP in both sexes; platelet numbers, total protein, albumin, total cholesterol, blood urea nitrogen, and calcium in females) occurred at 300 ppm (Japan Bioassay Research Center 1995), but a lack of reported numerical data and results of statistical analysis precludes interpretation of these end points. Absolute and relative liver and kidney weights in both sexes were significantly increased at 300 ppm. Additional findings included histopathological changes in the nasal cavity, liver, and testes. The nasal lesions included significantly increased incidences of respiratory metaplasia in the nasal gland (moderate severity) in males at 75 ppm (9/49, 12/49, 18/50, 11/49) and olfactory epithelium (slight severity) in males at 75 ppm (23/49, 30/49, 37/50, 22/49) and females at 300 ppm (7/50, 6/50, 2/49, 20/50); the effects in the males were not dose-related (i.e., incidences were increased at 75 ppm but not at 300 ppm). The incidence of centrilobular hepatocellular hypertrophy was significantly increased in male mice at 300 ppm (0/49, 0/49, 0/50, 34/49). Incidences of liver tumors were also increased at 300 ppm; these included hepatocellular carcinoma in males (12/49, 17/49, 16/50, 38/49) and females (2/50, 4/50, 2/49, 41/50), hepatocellular adenoma in females (2/50, 10/50, 6/49, 20/50), hepatoblastoma in males (0/49, 2/49, 0/50, 8/49) and females (0/50, 0/50, 0/49, 6/50), and histiocytic sarcoma in males (0/49, 3/49, 1/50, 6/49). Testicular mineralization was significantly increased in males at ≥75 ppm (27/49, 35/49, 42/50, 41/49) (Japan Bioassay Research Center 1995). The testicular mineralization was not considered to be a toxicologically significant effect (Aiso 2006) because (1) no signs of testicular toxicity were observed in mice exposed for 13 weeks (Aiso et al. 2005a), and (2) it was confined to the testicular capsules and testicular blood vessels and not observed in the testicular parenchyma, indicating that it is a finding commonly observed in aged mice independent of exposure to 1,4-DCB (Aiso 2006).

The results of this study indicate that moderate or severe eosinophilic changes in the nasal olfactory epithelium in female rats is the most sensitive toxic effect in the most sensitive species and sex. The NOAEL and LOAEL for these nasal lesions are 19.8 and 74.8 ppm, respectively.

<u>Dose and end point used for MRL derivation</u>:

[ ] NOAEL [ ] LOAEL [X] BMCL

As discussed below, a $BMCL_{10}$ of 9.51 ppm for increased incidences of nasal lesions in female rats is used as the point of departure for the MRL.

BMD analysis was conducted using the incidences for eosinophilic changes of moderate or greater severity in the nasal olfactory epithelium in female rats and the actual exposure concentrations. The data that were modeled are shown in Table A-4. Data for other end points were not modeled because the effects occurred at higher concentrations (nasal lesions and hepatocellular hypertrophy in mice, kidney lesions in rats) or were not toxicologically significant (testicular mineralization in mice). All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to the female rat nasal lesion incidence data. A 10% extra risk above the control incidence was selected as the BMR in the absence of a biological rationale for using an alternative BMR. As assessed by the chi-square goodness-of-fit statistic, all models provided adequate fits to the data (the quantal quadratic model was marginally adequate based on a chi-square p-value of 0.09 rather than the conventionally acceptable p-value of ≥0.1). The gamma, multistage, quantal linear, and Weibull models provided identical fit and were judged the

best-fitting models based on the lowest AIC value (Table A-5). These models each provided a benchmark concentration (BMC_{10}) of 14.08 ppm and lower 95% confidence limit ($BMCL_{10}$) of 9.51 ppm. A representative plot of the observed and predicted incidences of nasal lesions from the quantal linear model output is shown in Figure A-2. The $BMCL_{10}$ of 9.51 ppm was duration-adjusted to 1.70 ppm, converted to a HEC of 0.27 ppm, and divided by an uncertainty factor of 30 to derive an MRL of 0.01 ppm.

Table A-4. Incidences of Nasal Lesions in Female Rats Exposed to 1,4-Dichlorobenzene by Inhalation for 104 Weeks

Exposure concentration (ppm)	0	19.8	74.8	298.4
Nasal olfactory epithelial lesions (incidence)[a]	27/50[b]	29/50	39/50[c]	47/50[c]

[a]Lesions of moderate or greater severity.
[b]Significant trend of increasing response with increasing dose (Cochran-Armitage Test, performed by ATSDR).
[c]Significantly ($p \leq 0.05$) different from control value (Fisher's Exact Test performed by ATSDR).

Source: Aiso et al. 2005b

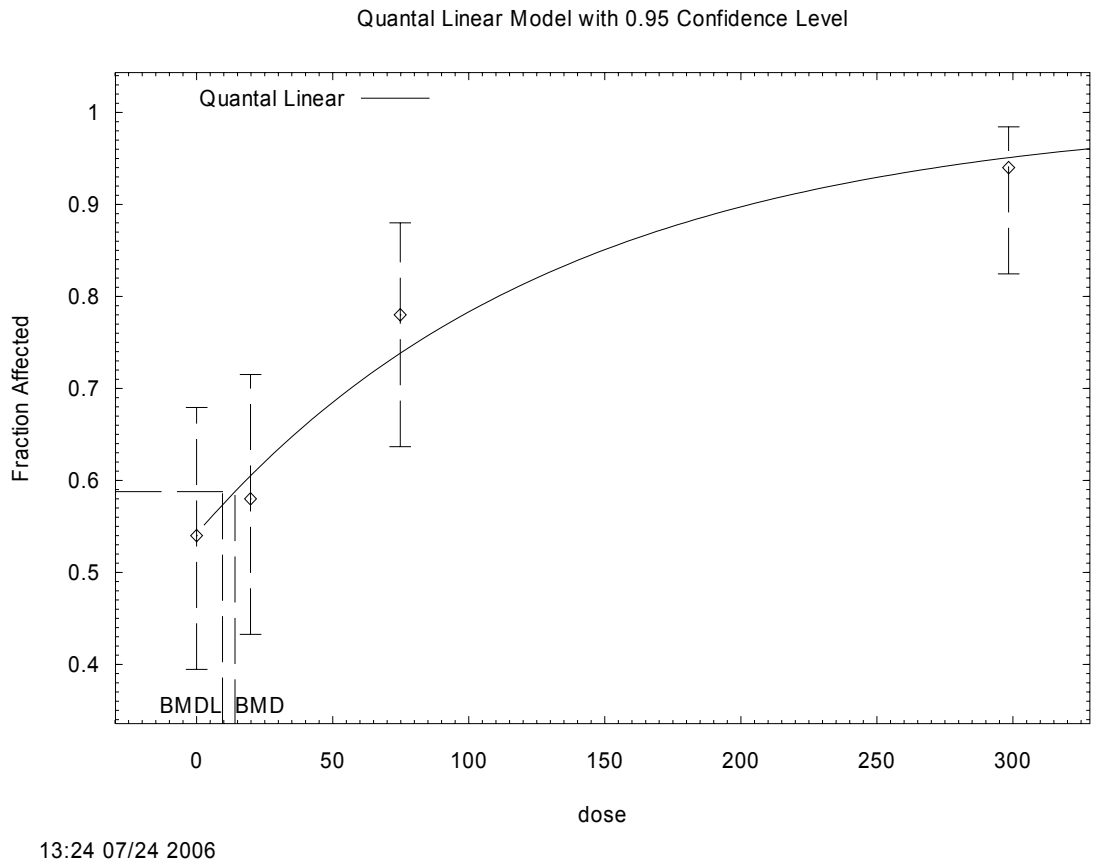
Table A-5. Modeling Results for Incidences of Nasal Lesions in Female Rats Exposed to 1,4-Dichlorobenzene by Inhalation for 104 Weeks

Model	Chi-square p-value[a]	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[b]	0.70	217.13	14.08	9.51
Logistic	0.51	217.79	19.43	13.90
Log-logistic[c]	0.74	218.52	15.45	4.12
Multi-stage[d]	0.70	217.13	14.08	9.51
Probit	0.42	218.21	22.17	16.70
Log-probit[c]	0.74	218.52	16.09	3.20
Quantal linear	0.70	217.13	14.08	9.51
Quantal quadratic	0.09	221.36	67.38	53.07
Weibull[b]	0.70	217.13	14.08	9.51

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas ≥0; Degree of polynomial=2

AIC = Akaike's Information Criteria; BMC_{10} = benchmark dose associated with a 10% extra risk; $BMCL_{10}$ = lower confidence limit (95%) on the benchmark dose

Figure A-2. Observed and Predicted Incidences of Nasal Lesions in Female Rats Exposed to 1,4-Dichlorobenzene for 104 Weeks*



*BMD = BMC; BMDL = BMCL; BMC and BMCL (in ppm) are associated with a 10% extra risk. The quantal linear model plot in this figure is identical to the plots produced by the gamma, multistage, and Weibull models.

Uncertainty Factors used in MRL derivation:

[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

A 3-fold uncertainty factor was used instead of a default 10-fold factor to extrapolate from rats to humans because the dosimetry adjustment (i.e., calculation of the human equivalent exposure for time and concentration [HEC]) addresses one of the two areas of uncertainty encompassed in an interspecies extrapolation factor. The dosimetric adjustment addresses the pharmacokinetic component of the extrapolation factor, but the pharmacodynamic area of uncertainty remains as a partial factor for interspecies uncertainty.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: For the nasal olfactory epithelium changes in female rats, 1,4-DCB was treated as a category 1 gas with effects in the extrathoracic region for purposes of calculating the HEC. Using EPA (1988, 1994b) reference values, the regional gas deposition ratio was calculated as follows (EPA 1994a):

$RGDR_{ET}$ = $[(V_E/SA_{ET})_A/(V_E/SA_{ET})_H]$
= $(0.24\ m^3/day/15cm^2)/(20\ m^3/day/200cm^2)$
= 0.16

where: $RGDR_{ET}$ = regional gas deposition ratio in the extrathoracic region
V_E = minute volume in rats $(V_E)_A$ or humans $(V_E)_H$
SA_{ET} = extrathoracic surface area in rats $(SA_{ET})_A$ or humans $(SA_{ET})_H$

The HEC was calculated by multiplying the rat $BMCL_{10\ ADJ}$ by the $RGDR_{ET}$ to yield a $BMCL_{10\ HEC}$ of 0.27 ppm, as follows:

$BMCL_{10\ HEC}$ = $BMCL_{10\ ADJ}$ x $RGDR_{ET}$
= 1.70 ppm x 0.16
= 0.27 ppm

Was a conversion used from intermittent to continuous exposure? The animal $BMCL_{10}$ value of 15.34 ppm was duration-adjusted for intermittent experimental exposure, as follows:

$BMCL_{10\ ADJ}$ = ($BMCL_{10}$) (hours/24 hours) (days/7 days)
= (9.51 ppm) (6 hours/24 hours) (5 days/7 days)
= 1.70 ppm

Other additional studies or pertinent information that lend support to this MRL: The only other information on the chronic inhalation toxicity of 1,4-DCB in animals is available from another study in rats and mice (Riley et al. 1980a, 1980b). In this study, rats of both sexes and female mice were exposed to 75 or 500 ppm of 1,4-DCB for 5 hours/day, 5 days/week for up to 76 weeks (rats) or 57 weeks (mice), followed by 32 weeks (rats) or 18–19 weeks (mice) without exposure. There were no exposure-related histopathological changes in the nasal cavity or other tissues in either species. Liver and kidney weights were increased in rats of both sexes at 500 ppm, but the toxicological significance is questionable due to the negative histopathology findings and the lack of related clinical chemistry effects. Evaluation of the mouse data is limited by reporting insufficiencies in the available summary of the study.

A limited amount of information is available on the long-term toxicity of inhaled 1,4-DCB in humans. Periodic occupational health examinations of workers who were exposed to 1,4-DCB for an average of 4.75 years (range 8 months to 25 years) showed no changes in standard blood and urine indices (Hollingsworth et al. 1956). The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. Occasional examination of the eyes showed no cataracts or any other lens changes. The odor and irritation properties were considered to be fairly good warning properties that should prevent excessive exposures, although the industrial experience indicated that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor. The data from this study are inadequate for chronic MRL derivation due to poor characterization of long-term exposure levels, insufficient investigation of systemic health end points, reporting and other study deficiencies. Although the available human information is insufficient for chronic MRL derivation, the human eye and nose irritation data are consistent with the nasal effects observed in the chronically exposed animals.

The NOAEL/LOAEL approach to MRL derivation results in an MRL of 0.02 ppm, similar to the 0.01 ppm value based on BMD analysis. Using the NOAEL of 19.8 ppm for moderate or severe changes

in the nasal olfactory epithelium in rats (Aiso et al. 2005b), the NOAEL was duration-adjusted for intermittent experimental exposure, as follows:

$$\begin{aligned} NOAEL_{ADJ} &= (NOAEL)\ (hours/24\ hours)\ (days/7\ days) \\ &= (19.8\ ppm)\ (6\ hours/24\ hours)\ (5\ days/7\ days) \\ &= 3.54\ ppm \end{aligned}$$

A HEC was calculated using EPA (1994a) inhalation dosimetric adjustment methodology. For the olfactory epithelium changes in rats, 1,4-DCB was treated as a category 1 gas with effects in the extrathoracic region. Using EPA (1988, 1994b) reference values, the regional gas deposition ratio was calculated as follows:

$$\begin{aligned} RGDR_{ET} &= [(V_E/SA_{ET})_A/(V_E/SA_{ET})_H] \\ &= (0.24\ m^3/day/15cm^2)/(20\ m^3/day/200cm^2) \\ &= 0.16 \end{aligned}$$

where: $RGDR_{ET}$ = regional gas deposition ratio in the extrathoracic region
V_E = minute volume in rats $(V_E)_A$ or humans $(V_E)_H$
SA_{ET} = extrathoracic surface area in rats $(SA_{ET})_A$ or humans $(SA_{ET})_H$

The rat $NOAEL_{ADJ}$ was multiplied by the $RGDR_{ET}$ to yield a $NOAEL_{HEC}$ of 0.57 ppm (3.54 ppm x 0.16), and the $NOAEL_{HEC}$ was divided by the uncertainty factor of 30 to derive an MRL of 0.02 ppm.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichlorobenzene (1,2-DCB)
CAS Numbers: 95-50-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: Rat

Minimal Risk Level: [0.7] mg/kg/day [ ] ppm

Reference: Robinson M, Bercz JP, Ringhand HP, et al. 1991. Ten and ninety-day toxicity studies of 1,2-dichlorobenzene administered by oral gavage to Sprague-Dawley rats. Drug Chem Toxicol 14(1&2):83-112.

Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were administered 1,2-DCB in corn oil by gavage in doses of 0, 37.5, 75, 150, or 300 mg/kg/day for 10 consecutive days. The doses were selected on the basis of a reported rat oral LD_{50} of 500 mg/kg. End points evaluated during the study included clinical signs, body weight, and food and water consumption. Evaluations at the end of the exposure period included hematology (five indices), serum chemistry (nine indices including AST, ALT, LDH, cholesterol, BUN, and creatinine), and selected organ weights (brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart, and testes or ovaries). Histological examinations were performed on various tissues including liver, kidneys, urinary bladder, heart, skin, muscle, bone, respiratory tract (nasal cavity with turbinates, lungs), nervous system (brain, sciatic nerve), immunological (spleen, thymus, lymph nodes), gastrointestinal (duodenum, ileum, jejunum, salivary gland, colon, cecum, rectum), endocrine (adrenal glands, pancreas), and reproductive (testes, seminal vesicles, prostate, ovaries) in the high-dose and control groups. Target organs identified in the high-dose groups were also histologically evaluated at the lower dose levels.

Effects noted in study and corresponding doses: No clinical signs or effects on survival were observed. Body weight gain was significantly reduced in the male rats at 300 mg/kg/day (final body weights were 10.9% lower than controls), but not in females, and there were no exposure-related changes in food consumption in either sex. Statistically significant changes in organ weights predominantly occurred at 300 mg/kg/day, including significantly decreased absolute spleen weight in both sexes, and decreased absolute heart, kidney, thymus, and testes weights in males. Liver weight (relative and absolute) was significantly increased in females at ≥150 mg/kg/day and in males at 300 mg/kg/day; compared to controls in the low- to high-dose females, absolute liver weights were 1.8, 9.0, 20.5, and 29.0% increased and relative liver weights were 6.8, 7.6, 21.7, and 34.5% increased. Clinical chemistry findings included significantly increased serum ALT in both sexes at 300 mg/kg/day and serum phosphorus in females at ≥150 mg/kg/day. Serum cholesterol was significantly increased in females at ≥37.5 mg/kg/day, but the toxicological significance is unclear because values were similar at all dose levels and showed no dose-response. Histopathological findings were limited to the liver and included necrosis that was slight in severity and significantly (p=0.04) increased in males at 300 mg/kg/day (4/10 compared to 0/10 in controls; incidences in the other dose groups were not reported, although the study authors indicated that target organs in the high-dose groups were histologically evaluated at the lower dose levels. Incidences of other hepatic lesions were not significantly increased, but included inflammation (characterized by lymphocyte and macrophage infiltrates) and degeneration of hepatocytes (characterized by varying degrees of fibrillar or vacuolated cytoplasm and swelling with intact cell membranes). Because incidences of histopathologic liver lesions were not reported for females, it is presumed that incidences in

the control and high-dose females were 0/10 and that the lower female dose groups were not assessed for liver lesions. This study identified a NOAEL of 75 mg/kg/day and LOAEL of 150 mg/kg/day for increased liver weight in female rats, as well as a LOAEL of 300 mg/kg/day for liver necrosis in male rats.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 67.73 mg/kg/day for increased liver weight in female rats is used as the point of departure for the MRL.

BMD analysis was conducted using the rat absolute liver weight data (Robinson et al. 1991) shown in Table A-6. The liver lesion data were not subjected to BMD analysis because incidences of liver necrosis were only reported for control and high-dose rats. Serum liver enzyme (ALT, AST, LDH) data were not subjected to BMD analysis because a statistically significant increase was noted only for serum ALT in the high-dose group of male rats and the magnitude of the increase (50% higher than the control serum ALT level) is not considered to be adverse.

Table A-6. Absolute Liver Weights in Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days

		Dose (mg/kg/day)				
Effect	Sex	0	37.5	75	150	300
Absolute liver weight (g)	M	9.8±0.70[a] n=10	10.30±0.94 n=10	9.90±0.62 n=10	10.21±1.29 n=10	11.00±0.83[b] n=10
	F	6.00±0.45 n=10	6.11±0.33 n=10	6.54±0.70 n=10	7.23±0.62[b] n=10	7.74±0.41[b] n=10

[a]Mean ± standard deviation
[b]Significantly (p≤0.05) different from control value

Source: Robinson et al. 1991

All continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the absolute liver weight data from male and female rats. One standard deviation increase from the control mean value was selected as the BMR in the absence of a biological rationale for using an alternative BMR. The modeling results are shown in Table A-7. Constant variance was assumed; the assumption was considered appropriate based on p-values >0.1 for the test of homogeneous variance. The linear, 2-degree polynomial, power, and Hill models provided adequate mean fit to the male rat liver weight data, as determined by p-values >0.1 for the test of mean fit. The linear model was determined to the best-fitting model (lowest AIC among all adequate model outputs) for the male rat liver weight data and provided a BMD_{1sd} of 249.04 mg/kg/day and a $BMDL_{1sd}$ of 158.55 mg/kg/day. For the female liver weight data, the linear and Hill models provided adequate mean fit (p-values >0.1). The linear model was the best-fitting model (lowest AIC) for the female rat liver weight data and provided a BMD_{1sd} of 84.67 mg/kg/day and a $BMDL_{1sd}$ of 67.73 mg/kg/day. Among the best-fitting model results for absolute liver weight in the male and female rats, the lowest (linear model-generated) $BMDL_{1sd}$ of 67.73 mg/kg/day for increased absolute liver weight in female rats is selected as the point of departure for deriving the MRL. The $BMDL_{1sd}$ of 67.73 mg/kg/day was divided by an uncertainty factor of 100 to derive an MRL of 0.7 mg/kg/day.

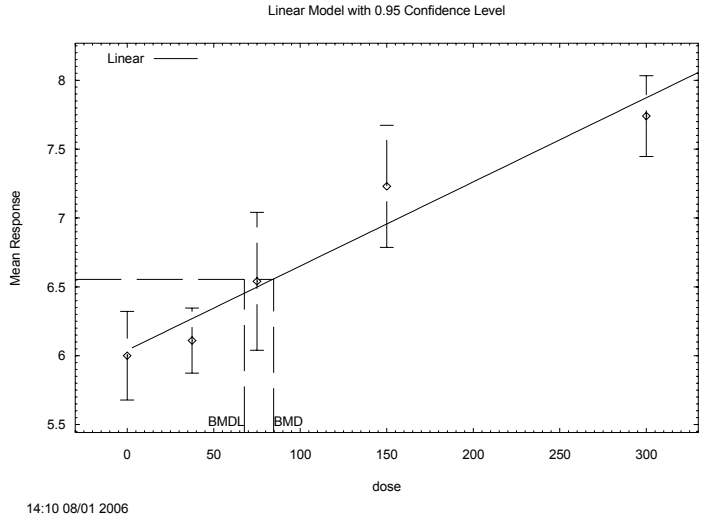
Table A-7. Model Predictions for Increased Absolute Liver Weight in Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Males					
Linear[b]	0.15	0.48	41.40	249.04	158.55
Polynomial[b,c,d]	0.15	0.38	42.87	274.93	164.78
Power[b,e]	0.15	0.38	44.86	281.79	164.87
Hill[b,f]	0.15	0.17	46.80	180.01	No value
Females					
Linear[b]	0.12	0.19	-11.85	84.67	67.73
Polynomial[b,c,d,]	0.12	0.09	-11.85	84.67	67.73
Power[b,e]	0.12	0.09	-7.85	84.67	67.73
Hill[b,f]	0.12	0.84	-10.55	71.51	43.18

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Constant variance assumed
[c]Restriction = non-negative
[d]2-degree polynomial
[e]Restrict power >=1
[f]Restrict n>1
[g]Non-homogeneous variance assumed

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose associated with one standard deviation increase above control mean; BMDL = lower confidence limit (95%) on the benchmark dose

Figure A-3. Observed and Predicted Mean Absolute Liver Weight in Female Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days*



*The BMD and BMDL (in mg/kg/day) represent a 1 standard deviation increase in mean absolute liver weight from the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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: Information on effects of acute oral exposure to sublethal doses of 1,2-DCB essentially consists of findings in three systemic toxicity studies in rats and mice and one developmental toxicity study in rats (NTP 1985; Rimington and Ziegler 1963; Robinson et al. 1991; Ruddick et al. 1983). These studies administered the compound by gavage and collectively identify the liver as the most sensitive target. Severe liver damage, characterized by intense necrosis and fatty changes as well as porphyria, occurred in rats administered 455 mg/kg/day for 15 consecutive days (Rimington and Ziegler 1963). Rats that were exposed to 300 mg/kg/day for 10 consecutive days had hepatic effects that included necrosis and increased serum ALT (Robinson et al. 1991). Hepatocellular degeneration and necrosis occurred in mice that were exposed to 250 or 500 mg/kg/day for 14 consecutive days (NTP 1985). The 15-day rat and 14-day mouse studies are limited by small numbers of animals (3–5 per dose) and lack of a NOAEL due a single dose level (Rimington and Ziegler 1963) or lack of histopathology evaluations at doses lower than the LOAEL (NTP 1985). The 10-day study (Robinson et al. 1991) is the most appropriate basis for MRL derivation because it is well designed, included four dose levels, and provides dose-response data for several hepatic end points.

The NOAEL/LOAEL approach to MRL derivation results in an MRL similar to the 0.7 mg/kg/day value based on BMD analysis. Using the 75 mg/kg/day NOAEL for increased liver weight (Robinson et al. 1991) and the uncertainty factor of 100, the NOAEL/LOAEL approach yields an MRL of 0.8 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichlorobenzenes (1,2-DCB)
CAS Numbers: 95-50-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 17
Species: Rat

Minimal Risk Level: [0.6] mg/kg/day [ ] ppm

Reference: NTP. 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 255. NIH Publication No. 86-2511.

Experimental design: Groups of 10 male and 10 female F344/N rats and 10 male and 10 female $B6C3F_1$ mice were administered 1,2-DCB (>99% pure) in corn oil by gavage in doses of 0, 30, 60, 125, 250, or 500 mg/kg on 5 days/week for 13 weeks. Evaluations included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine volume, urine uroporphyrins and coproporphyrins, liver porphyrins, organ weights, and necropsies in all groups of animals. Complete histological examinations were performed on all control and high-dose animals; histology exams in lower dose groups were limited to liver, kidneys and thymus at 125 and 250 mg/kg/day.

Effects noted in study and corresponding doses: Effects in the rats included necrosis of individual hepatocytes at ≥250 mg/kg/day and centrilobular degeneration at 500 mg/kg/day; total incidences of these lesions at 0, 125, 250, and 500 mg/kg/day were 0/10, 1/10, 4/9, and 8/10 in males, and 0/10, 3/10, 5/10, and 7/8 in females. Relative liver weights were significantly increased at 125, 250, and 500 mg/kg/day in the males (8, 17, and 45% higher than controls) and females (8, 15, and 30%); increased relative liver weights were not seen at lower doses in either sex. There were no increases in serum levels of liver enzymes [ALT, AP, or GGPT] at any dose in either sex. Serum cholesterol was significantly increased in males at ≥30 mg/kg/day (50.0, 17.6, 26.5, 70.6, and 109% higher than controls in the low- to high-dose groups, not significant at 60 mg/kg/day) and females at ≥125 mg/kg/day (12.2, 12.2, 32.6, 26.5, and 51.0%). Although increases in serum cholesterol were observed at levels as low as 30 mg/kg/day, the toxicological significance is unclear because there was no clear dose-response unless the increase at 30 mg/kg/day is considered to be outlying. Urinary concentrations of uroporphyrin and coproporphyrin were 3–5 times higher than controls in the 500 mg/kg/day males and females, but this increase was not considered indicative of porphyria because total porphyrin concentration in the liver was not altered at any dose level and no pigmentation indicative of porphyria was observed by ultraviolet light at necropsy. The increases in relative liver weight and liver lesions seen in both sexes at 125 mg/kg/day are believed to represent the beginning of adverse hepatic effects, and are thus designated a minimal LOAEL for this study. The NOAEL is therefore 60 mg/kg/day.

In the mice, no compound-related histopathological changes were observed in either sex at 0 and 125 mg/kg/day, or in females at 250 mg/kg/day. Lesions that were significantly increased included necrosis of individual hepatocytes, hepatocellular degeneration and/or pigment deposition in 4/10 males at 250 mg/kg/day, and centrilobular necrosis, necrosis of individual hepatocytes, and/or hepatocellular degeneration in 9/10 males and 9/10 females at 500 mg/kg/day. Relative liver weights were significantly increased at 500 mg/kg/day in both sexes, but there were no exposure-related changes in serum levels of ALT, AP, or GGPT in either sex at any dose (no other clinical chemistry indices were examined in the

mice). Based on the liver lesion data, the NOAEL and LOAEL in mice are 125 and 250 mg/kg/day, respectively.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 89.27 mg/kg/day for increased relative liver weight in female rats is used as the point of departure for the MRL.

Benchmark dose analysis was conducted using the male and female rat and male mouse liver lesion incidence data summarized in Table A-8. Dichotomous models available in the EPA Benchmark Dose Software were fit to data for incidences of liver lesions (single cell necrosis, centrilobular necrosis, and/or hepatocellular degeneration) in male and female rats (combined) and male mice. Because there were no apparent differences in sensitivity to 1,2-DCB among the male and female rats, the liver lesion data were combined to increase the statistical power for BMD analysis. For each data set (combined incidences in male and female rats and incidences in male mice), the Chi-square p-value and AIC were used to select the best fitting model from which BMDs and their lower 95% confidence limits (BMDLs) were calculated, using a BMR of 10% extra risk.

Table A-8. Incidences of Liver Lesions in Rats and Mice Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks

Lesions: Individual cell or focal necrosis; centrilobular degeneration in high-dose group	Dose (mg/kg/day)					
	0	30	60	125	250	500
Male rat	0/10	ND	ND	1/10	4/9[a]	8/10[a]
Female rat	0/10	ND	ND	3/10	5/10[a]	7/8[a]
Combined (male and female)	0/20	ND	ND	4/20[a]	9/19[b]	15/18[b]
Male mouse	0/10	ND	ND	0/10	4/10[a]	9/10[a]

[a]Significantly ($p<0.05$) different from control; Fisher Exact Test performed by ATSDR
[b]Significantly ($p<0.01$) different from control; Fisher Exact Test performed by ATSDR

ND = no histological examinations conducted in this group

Source: NTP 1985

All models provided adequate fit to liver lesion data for male and female rats combined (Table A-9). The best-fitting model (lowest AIC) was the quantal quadratic model, which provided a BMD_{10} of 108.71 mg/kg/day and a $BMDL_{10}$ of 92.08 mg/kg/day. The log-probit model was determined to be the best-fitting model for the male mouse data and provided a BMD_{10} of 176.05 mg/kg/day and $BMDL_{10}$ of 114.58 mg/kg/day.

Table A-9. BMD Model Results of Incidence Data for Liver Lesions in Male and Female Rats (Combined) and Male Mice Exposed to 1,2-Dichlorobenzene for 13 Weeks

Model	Chi-square p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Male and female rats combined				
Gamma[b]	0.99	66.53	81.08	31.38
Logistic	0.34	69.78	112.08	81.57
Log Logistic[c]	0.94	66.64	89.36	39.14
Multi-stage[d]	0.99	66.55	66.22	31.31
Probit	0.38	69.33	106.79	78.36
Log-probit[c]	0.94	66.64	92.42	54.15
Quantal-linear	0.67	66.20	38.18	27.93
Quantal-quadratic	0.64	66.02	108.71	92.08
Weibull	0.99	66.52	75.28	31.39
Male mice				
Gamma[b]	0.75	24.78	172.36	102.08
Logistic	0.44	26.24	168.53	106.72
Log-logistic[c]	0.81	24.62	175.35	110.25
Multi-stage[d]	0.48	24.57	116.66	63.82
Probit	0.48	25.93	167.39	102.39
Log-probit[c]	0.86	24.42	176.05	114.58
Quantal-linear	0.14	30.41	44.73	28.59
Quantal-quadratic	0.69	24.57	116.66	91.67
Weibull	0.61	25.46	158.84	86.28

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas >=0; lowest degree polynomial (2-degree) with an adequate fit

AIC = Akaike's Information Criteria; BMD_{10} = benchmark dose based on a benchmark response of 10%; $BMDL_{10}$ = lower confidence limit (95%) on the BMD_{10}

BMD analysis was also conducted using the relative liver weight data for male and female rats shown in Table A-10). Continuous variable models in the EPA Benchmark Dose Software were fit to the liver weight data, and one standard deviation from the control mean was selected as the BMR in the absence of a biological rationale for using a different BMR. For the male rat relative liver weight data, results of model runs using constant variance indicated that non-homogeneous variance was more appropriate. However, selection of non-homogeneous variance resulted in inadequate mean fits (p-value <0.04) from the linear, polynomial, and power models, and the Hill model would not generate an output. For the relative liver weight data of the female rats, constant variance was appropriate (p-value >0.1) and adequate mean fits were obtained from the linear, polynomial, and power models (Table A-11). The Hill model would not generate an output for the female relative liver weight data. Among the adequate mean fits, the linear model provided the lowest AIC and was therefore selected as the best-fitting model for the

female rat relative liver weight data (Table A-11, Figure A-4), which resulted in a BMD_{1sd} of 108.15 mg/kg/day and a $BMDL_{1sd}$ of 89.27 mg/kg/day.

Table A-10. Relative Liver Weight Data for Male and Female Rats Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks

	Mean measured exposure concentration (ppm)					
	0	30	60	125	250	500
Males						
Group size	9	9	10	9	9	10
Relative liver weight[a]	3.18	3.28	3.10	3.43[b]	3.72[b]	4.61[b]
Standard deviation	0.20	0.22	0.15	0.22	0.29	0.47
Females						
Group size	10	10	10	10	10	8
Relative liver weight[a]	2.90	2.98	2.92	3.13[b]	3.33[b]	3.78[b]
Standard deviation	0.20	0.15	0.16	0.20	0.18	0.30

[a]Mean value
[b]Significantly different ($p<0.05$) from control group

Source: NTP 1985

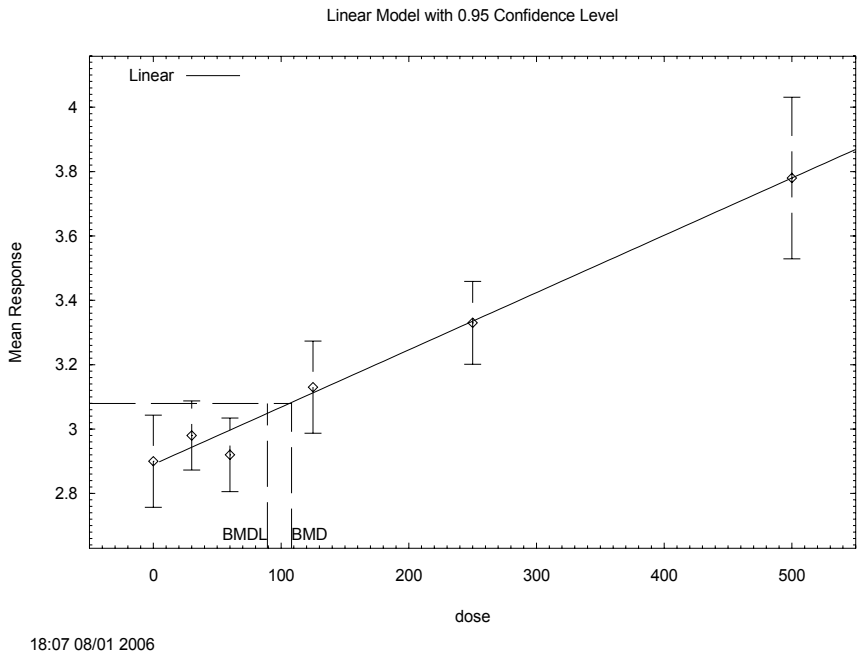
Table A-11. Model Predictions for Relative Liver Weight in Female Rats Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (ppm)	$BMDL_{1sd}$ (ppm)
Linear[b]	0.338	0.719	-129.0910	108.15	89.27
2-Degree polynomial[b,c]	0.338	0.559	-127.1169	112.34	89.34
Power[b,d]	0.338	0.5679	-125.1600	116.96	89.47

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Power restricted to >=1

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation from the control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}

Figure A-4. Observed and Predicted Mean Relative Liver Weights in Female Rats Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 1 standard deviation increase above the control mean

The $BMDL_{1sd}$ of 89.27 mg/kg/day from the best-fitting modeling results of the female rat relative liver weight data is lower than the $BMDL_{10}$ of 92.08 mg/kg/day from the best-fitting modeling results of liver lesion incidences in the male and female rats combined and the $BMDL_{10}$ of 114.58 mg/kg/day from the best-fitting model results of liver lesion incidences in the male mice. Therefore, the $BMDL_{1sd}$ of 89.27 mg/kg/day for increased relative liver weight in the female rats is selected as the point of departure for the MRL. The $BMDL_{1sd}$ of 89.27 mg/kg/day was duration-adjusted to 63.76 mg/kg/day and divided by an uncertainty factor of 100 to yield an MRL of 0.6 mg/kg/day.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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? The $BMDL_{1sd}$ of 89.27 mg/kg/day was duration-adjusted for intermittent exposure, as follows (EPA 1994k):

$$BMDL_{1sd\ ADJ} = (BMDL_{1sd})\ (\text{days}/7\ \text{days})$$
$$= (89.27\ \text{mg/kg/day})\ (5\ \text{days}/7\ \text{days})$$
$$= 63.76\ \text{mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL: Information on effects of intermediate-duration oral exposure to 1,2-DCB are available from three intermediate studies in rats and mice identifying the liver as the most sensitive target of toxicity (Hollingsworth et al. 1958; NTP 1985; Robinson et al. 1991). Incidences of degenerative liver lesions were significantly increased in rats and mice exposed to ≥250 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), 376 mg/kg/day, 5 days/week for 192 days (Hollingsworth et al. 1958; NTP 1985), and 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991). Necrotic lesions also occurred in several rats at 125 mg/kg/day (1/10 males, 3/10 females) in the NTP (1985) study, but the increase was not statistically significant. Other hepatic findings in rats exposed to lower doses (125–188 mg/kg/day for ≥13 weeks) in these studies included small increases in relative liver weight and serum levels of ALT, cholesterol, and serum protein, and decreases in serum triglycerides. Increased serum ALT is an inconsistent finding because it was induced in rats exposed to ≥100 mg/kg/day for 90 days (Robinson et al. 1991), but not in rats exposed to ≥125 mg/kg/day for 13 weeks (NTP 1985). Additionally, the increase in serum ALT was not dose-related, and serum levels of other liver-associated enzymes were not increased in either the Robinson et al. (1991) study (AST, LDH, and AP) or the NTP (1985) study (AP and gamma-glutamyltranspeptidase [GGTP]). The lowest LOAEL is 125 mg/kg/day, which is a minimal LOAEL for increased liver weight in rats in the NTP (1985) study; the corresponding NOAEL is 60 mg/kg/day.

The NOAEL/LOAEL approach to MRL derivation results in a lower MRL than the 0.6 mg/kg/day value based on benchmark dose analysis. Using the 60 mg/kg/day NOAEL for increased liver weight in rats (NTP 1985), the NOAEL is duration-adjusted to 42.9 mg/kg/day (60 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.4 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichlorobenzene (1,2-DCB)
CAS Numbers: 95-50-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 31
Species: Mouse

Minimal Risk Level: [0.3] mg/kg/day [ ] ppm

Reference: NTP. 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 255. NIH Publication No. 86-2511.

Experimental design: Groups of 50 male and 50 female F344/N rats and 50 male and 50 female $B6C3F_1$ mice were administered 1,2-DCB (>99% pure) in corn oil by gavage in doses of 0, 60, or 120 mg/kg on 5 days/week for 103 weeks. Evaluations included clinical signs, body weight, and gross observations in all groups of animals. Complete histological examinations were performed on all animals, and included evaluations of at least 30 tissues.

Effects noted in study and corresponding doses: Survival was significantly reduced in high-dose male rats, relative to control male rats, but not in the low-dose group or in any group of female rats. Mean body weights of high-dose male rats were slightly, but not statistically significantly, lower than those of controls throughout the study; the mean body weights of low-dose males were comparable to those of controls, and exposed female rats had higher body weights than controls. No changes in clinical signs were reported for either sex of rats. No increases in gross observations were reported on necropsy, and no changes in nonneoplastic lesions were seen in the liver, kidney, bone marrow, spleen, thymus, or other organs or tissues in exposed rats.

In the mice, no statistically significant differences in survival were seen in either sex at any dose level. Mean body weights were similar to controls for all treated groups of male and female mice. In male mice, there was a dose-related increase in the incidence of renal tubular regeneration (controls: 8/48; low dose: 12/50; high dose: 17/49); the increase was statistically significant (Fisher's Exact Test, performed by ATSDR) in the high-dose group. No other increases were observed in nonneoplastic lesions of the liver, bone marrow, spleen, or any other evaluated organ or tissue.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{10}$ of 43.04 mg/kg/day for increased incidences of renal tubular regeneration in male mice is used as the point of departure for the MRL.

BMD analysis was conducted using the kidney lesion incidence data summarized in Table A-12. All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to the male mouse incidence data for renal tubule regeneration. A 10% extra risk above the control incidence was selected as the BMR in the absence of a biological rationale for using an alternative BMR. The modeling results are shown in Table A-13. The gamma, log-logistic, and Weibull models outputs failed to provide Chi-

square p-values for goodness of fit statistic (Chi-square = 0; degrees of freedom = 0) and were therefore not considered for selection of a point of departure. The other models (logistic, multistage, probit, log-probit, quantal-linear, and quantal-quadratic) provided adequate fits to the data (Chi-square p-values ≥0.1). The logistic model was the best-fitting model for the renal tubule regeneration incidence data, based on the lowest AIC, and provided a BMD_{10} of 62.96 mg/kg/day and a $BMDL_{10}$ of 43.04 mg/kg/day (Table A-13, Figure A-5). The $BMDL_{10}$ of 43.04 mg/kg/day was duration-adjusted to 30.74 mg/kg/day and divided by an uncertainty factor of 100 to yield an MRL of 0.3 mg/kg/day.

Table A-12. Incidences of Kidney Lesions in Male Mice Orally Exposed to 1,2-Dichlorobenzene for 103 Weeks

	Dose (mg/kg/day)		
Lesion: Regeneration of kidney tubule cells	0	60	120
Incidence/group size	8/48	12/50	17/49[a]

[a]Significantly (p<0.05) different from control; Fisher Exact Test performed by ATSDR

Source: NTP 1985

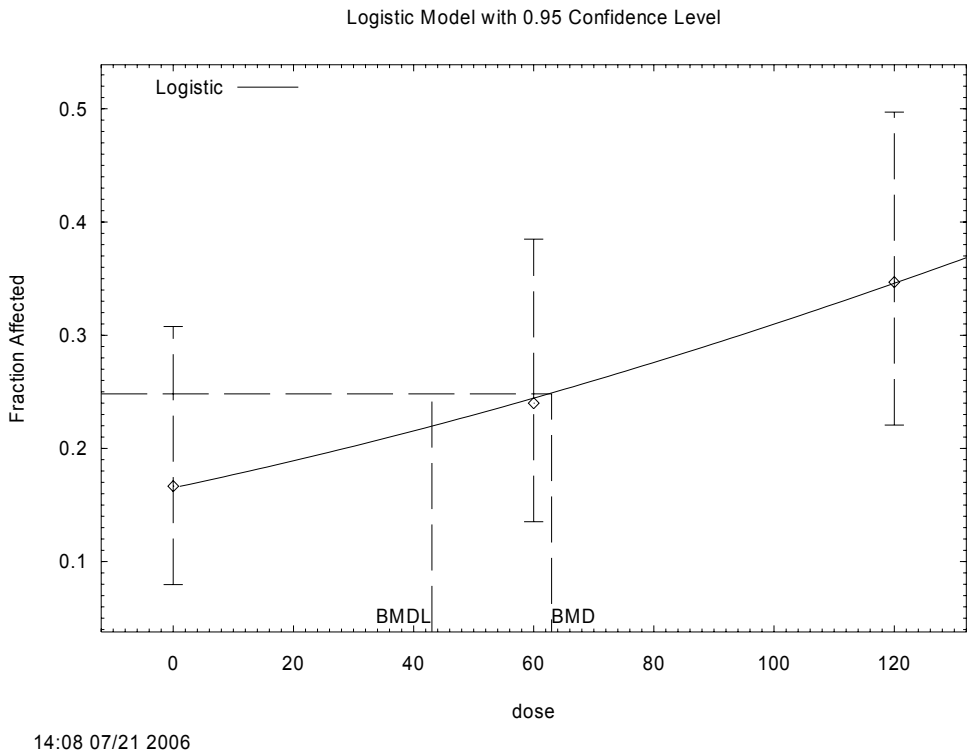
Table A-13. BMD Modeling of Incidence Data for Kidney Lesions in Male Mice Exposed to 1,2-Dichlorobenzene for 103 Weeks

Model	Chi-square p-value	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[a]	NA	167.62	65.92	29.80
Logistic	0.94	165.63	62.96	43.04
Log-logistic[b]	NA	167.62	65.85	26.33
Multi-stage[c]	0.77	165.71	53.90	29.58
Probit	0.91	165.64	61.60	41.20
Log-probit[b]	0.84	165.67	72.33	46.85
Quantal-linear	0.77	165.71	53.90	29.58
Quantal-quadratic	0.74	165.73	79.20	57.20
Weibull	NA	167.62	66.03	29.80

[a]Restrict power >=1
[b]Slope restricted to >1
[c]Restrict betas >=0; lowest degree polynomial (1-degree) providing adequate fit

AIC = Akaike's Information Criteria; BMD_{10} = benchmark dose associated with 10% extra risk; $BMDL_{10}$ = lower confidence limit (95%) on the benchmark dose; NA = Chi-square p-value not applicable (Chi-square = 0; degrees of freedom = 0)

Figure A-5. Observed and Predicted Incidences of Kidney Lesions in Male Mice Exposed to 1,2-Dichlorobenzene for 103 Weeks*



*BMD and BMDL (in mg/kg/day) are associated with a 10% extra risk.

Source: NTP 1985

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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? The $BMDL_{10}$ of 43.04 mg/kg/day was duration-adjusted for intermittent exposure, as follows (EPA 1994k):

$$BMDL_{10\ ADJ} = (BMDL_{10})\ (\text{days}/7\ \text{days})$$
$$= (43.04\ \text{mg/kg/day})\ (5\ \text{days}/7\ \text{days})$$
$$= 30.74\ \text{mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL: No other studies were located that evaluated effects on renal tissues following chronic oral exposure to 1,2-DCB.

The NOAEL/LOAEL approach to MRL derivation results in a similar chronic-duration oral MRL value as the benchmark dose approach. Using the NOAEL of 60 mg/kg/day for increased incidence of renal tubular regeneration, the NOAEL is duration-adjusted to 43 mg/kg/day (60 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.4 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichlorobenzene (1,3-DCB)
CAS Numbers: 541-73-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 2
Species: Rat

Minimal Risk Level: [0.4] mg/kg/day [ ] ppm

Reference: McCauley PT, Robinson M, Daniel FB, et al. 1995. Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem Toxicol 18(2 & 3):201-221.

Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were administered 1,3-DCB in gavage doses of 0, 37, 147, 368, or 735 mg/kg/day in corn oil for 10 consecutive days. End points evaluated during the study included clinical signs, survival, body weight, and food and water consumption. At the end of the study, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), and selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads). Gross pathology was evaluated in all animals, and comprehensive histological examinations were performed in the high dose and control groups; histology in the lower dose groups was limited to the liver. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

Effects noted in study and corresponding doses: No compound-related deaths or overt clinical signs were observed. Body weight was significantly reduced in both sexes at 735 mg/kg/day (20 and 13% lower than controls in males and females, respectively). Food consumption was significantly decreased at 735 mg/kg/day in males (12%, normalized by body weight), and water consumption was significantly increased (8–13%) in females at ≥735 mg/kg/day. The hematological evaluation showed 8% decreased MCV in females at 735 mg/kg/day. The clinical chemistry analyses showed statistically significant changes in several indices, but serum cholesterol was the only end point that had values that exceeded the reference range. Serum cholesterol was significantly increased in females at 368 and 735 mg/kg/day (94 and 63% higher than controls, respectively), as well as in males at 368 and 735 mg/kg/day (79 and 84% higher than controls, respectively). Relative liver weight was significantly increased in males at ≥147 mg/kg/day and females at ≥368 mg/kg/day; increases in the males were 9.1, 31.3, 50.63, and 32.5% higher than controls in the low- to high-dose groups. Other significant changes in relative organ weight included decreased spleen weight in females at ≥368 mg/kg/day and in males at 735 mg/kg/day, decreased thymus weight in both sexes at 735 mg/kg/day, and decreased testes weight in males at 735 mg/kg/day. Absolute organ weights were not reported. Histological changes primarily occurred in the liver, particularly centrilobular hepatocellular degeneration at ≥368 mg/kg/day. This lesion was characterized by varying degrees of cytoplasmic vacuolization and swelling with intact membranes, and occurred in the 368 and 735 mg/kg/day groups in 2/10 and 9/10 males, respectively, and in 6/10 and 10/10 females, respectively; incidences in the other groups were not reported, but are presumed to be 0/10. Other hepatic alterations included hepatocellular necrosis that was sporadically noted in the 147, 368, and 735 mg/kg/day groups. This change was usually minimal to mild, and tended to increase in incidence and severity in the males in a dose-related manner; however, incidences were not reported. The only other reported histological change was atrophy of the thymus, characterized by loss of normal

differentiation between medulla and cortex. The thymic atrophy was observed in 2/10 males (both marked in severity) and 2/9 females (both mild in severity) at 735 mg/kg/day; this change was not observed in controls, and the other dosed groups were not examined. The 147 mg/kg/day dose is a LOAEL based on the >30% increase in relative liver weight in male rats. The NOAEL for increased liver weight is 37 mg/kg/day.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 36.32 mg/kg/day for increased liver weight in female rats is used as the point of departure for the MRL.

BMD analysis was conducted on hepatic effects data in the male and female rats of the McCauley et al. (1995) study. The liver effects data modeled included the incidences of hepatocellular degeneration, absolute liver weights, and mean serum cholesterol levels shown in Table A-14.

Table A-14. Liver Effects Observed in Rats Orally Exposed to 1,3-Dichlorobenzene for 10 Days

		Dose (mg/kg/day)				
Effects	Sex	0	37	147	368	735
Centrilobular hepatocellular degeneration	M	0/10[a]	0/10[a]	0/10[a]	2/10	9/10[b]
	F	0/10[a]	0/10[a]	0/10[a]	6/10[b]	10/10[b]
Absolute liver weight (g)	M	11.04±1.00 n=10	12.06±1.56 n=10	14.5±2.30[b] n=9	16.63±1.62[b] n=10	14.63±2.26[b] n=9
	F	7.68±0.75 n=10	8.12±0.77 n=10	9.18±0.99 n=9	11.90±1.19[b] n=10	12.66±2.55[b] n=9
Mean serum cholesterol (mg/dL)	M	63.0±10.2 n=10	63.6±3.7 n=10	92.4±20.9 n=10	112.5±16.3[b] n=9	116.0±49.6[b] n=10
	F	64.8±12.2 n=8	73.3±10.8 n=10	87.9±13.8 n=9	125.4±27.0[b] n=10	105.7±16.6[b] n=9

[a]Incidences of centrilobular hepatocellular degeneration were not reported for the 0, 37, and 147 mg/kg/day dose groups, but are assumed to be 0/10 each because the lesion was only reported present in the two highest dose groups.
[b]Significantly (p≤0.05) different from control value.

Source: McCauley et al. 1995

All dichotomous variable models available in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the incidence data for hepatocellular degeneration in male and female rats. A BMR of 10% extra risk was selected in the absence of a biological rationale for selecting an alternative BMR. The modeling results are shown in Table A-15. All dichotomous models provided adequate fit to the male and female hepatocellular degeneration incidence data, as determined by Chi-square p-values >0.1 (Table A-15). The log-probit model was determined to be the best-fitting (lowest AIC) model for the male data and provided a BMD_{10} of 319.18 mg/kg/day and a $BMDL_{10}$ of 207.86 mg/kg/day. The log-logistic model was determined to be the best-fitting (lowest AIC) model for the female data and provided a BMD_{10} of 318.46 mg/kg/day and a $BMDL_{10}$ of 159.37 mg/kg/day.

Table A-15. Modeling Results for Incidences of Centrilobular Degeneration in Male and Female Rats Orally Exposed to 1,3-Dichlorobenzene for 10 Days

Model	Chi-square p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Males				
Gamma[b]	0.9997	20.53	314.37	196.42
Logistic	0.9386	21.15	322.99	215.61
Log-logistic[c]	0.9992	20.55	317.16	206.86
Multi-stage[d]	0.9895	20.72	305.72	156.48
Probit	0.9787	20.81	316.14	205.06
Log-probit[c]	1.0000	20.51	319.18	207.86
Quantal linear	0.1153	28.95	82.93	51.49
Quantal quadratic	0.7150	21.46	190.83	148.00
Weibull[b]	0.9918	20.69	306.04	182.80
Females				
Gamma[b]	1.00	15.48	251.73	145.75
Logistic	1.00	17.46	338.16	167.41
Log-logistic[c]	1.00	15.46	318.46	159.37
Multi-stage[d]	0.97	15.92	216.50	124.71
Probit	1.00	17.46	310.54	153.36
Log-probit[c]	1.00	17.46	303.18	153.81
Quantal linear	0.13	28.04	45.74	29.88
Quantal quadratic	0.75	19.06	128.58	99.32
Weibull[b]	1.00	17.46	313.61	138.53

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas ≥0; Degree of polynomial=2

AIC = Akaike's Information Criteria; BMD_{10} = benchmark dose associated with a 10% extra risk; $BMDL_{10}$ = lower confidence limit (95%) on the benchmark dose

All continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the mean absolute liver weight data and mean serum cholesterol level data from the male and female rats. A BMR of 1 standard deviation increase above the control mean was selected in the absence of a biological rationale for using an alternative BMR. None of the available models provided adequate mean fit to the male rat absolute liver weight data or the female rat serum cholesterol data, based on p-values <0.01 for mean fit. Modeling of the male rat serum cholesterol data resulted in failed tests for both constant and non-homogeneous variance.

For the female rat absolute liver weight data, results of testing for constant and non-homogeneous variance indicated that a non-homogeneous variance assumption was appropriate. The modeling results are shown in Table A-16. Based on this assumption, the linear, 2-degree polynomial, and Hill models provided adequate mean fit to the female rat absolute liver weight data. The power model provided a p-value of 0.093, which was considered adequate, although a p-value >0.1 is the conventional goodness-

of-fit standard. Although the Hill model provided adequate mean fit, it failed to determine a BMDL and was rejected from further consideration for selection of a point of departure for deriving an acute-duration oral MRL. The best-fitting model for the female rat absolute liver weight data was the 2-degree polynomial model (lowest AIC), which provided a BMD_{1sd} of 51.83 mg/kg/day and a $BMDL_{1sd}$ of 36.32 mg/kg/day.

In summary, BMD analysis of liver effects in the male and female rats of the principal study (McCauley et al. 1995) resulted in a $BMDL_{10}$ of 207.86 mg/kg/day for hepatocellular degeneration in male rats (best-fitting [log-probit] model), a $BMDL_{10}$ of 159.37 mg/kg/day for hepatocellular degeneration in female rats (best-fitting [log-probit] model), and a $BMDL_{1sd}$ of 36.32 mg/kg/day for absolute liver weight changes in female rats (best-fitting [2-degree polynomial] model). Using a conservative approach, the $BMDL_{1sd}$ of 36.32 mg/kg/day for absolute liver weight changes in female rats (Table A-16, Figure A-6) is selected as the point of departure for deriving an MRL. The $BMDL_{1sd}$ of 36.32 mg/kg/day was divided by an uncertainty factor of 100 to derive an MRL of 0.4 mg/kg/day.

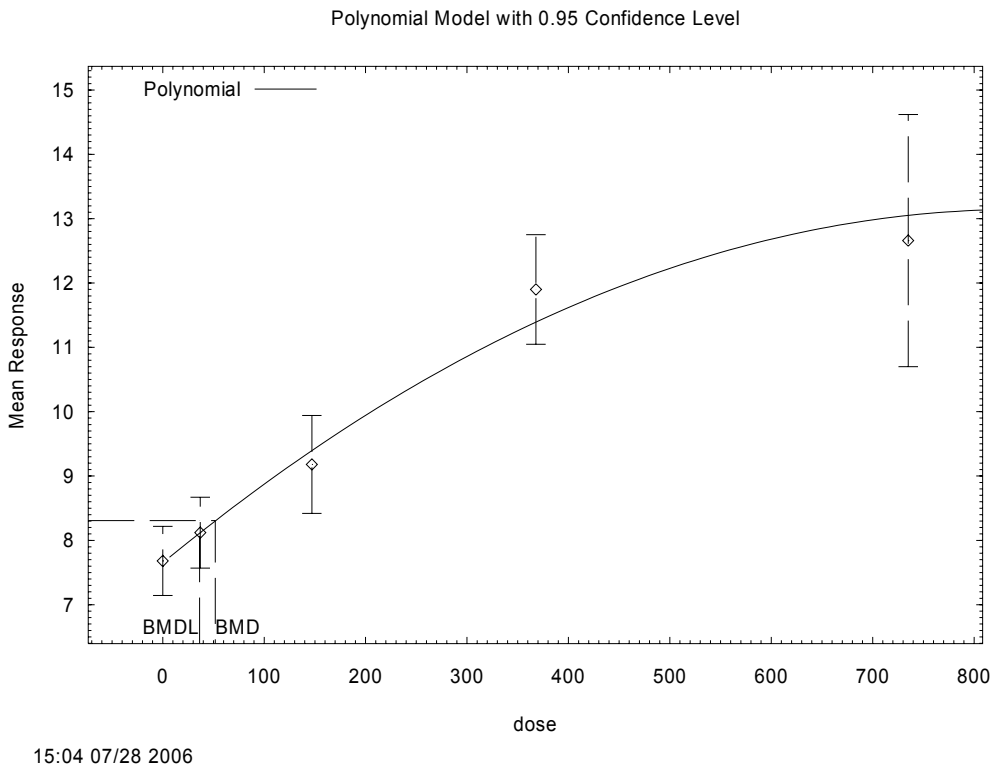
Table A-16. Modeling Results for Absolute Liver Weight Data in Female Rats Orally Exposed to 1,3-Dichlorobenzene for 10 Days

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Linear[b,c]	0.0002	NA	NA	NA	NA
Linear[c,d]	0.36	0.15	68.39	76.09	55.09
Polynomial[c,e]	0.36	0.62	66.046	51.83	36.32
Power[d,f]	0.29	0.093	70.39	76.08	55.09
Hill[d,g]	0.36	0.37	67.87	78.40	No value

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Non-homogeneous variance assumed
[e]Lowest degree polynomial (2-degree) providing adequate fit
[f]Restrict power >=1
[g]Restrict n>1

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose associated with one standard deviation increase above control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}; F= BMDL computation failed due to bad completion code in Optimization routine; NA = not applicable, as model does not provide adequate fit

Figure A-6. Observed and Predicted Liver Weights in Female Rats Exposed to 1,3-Dichlorobenzene for 10 Days*



*BMD and BMDL (in mg/kg/day) are for a 1 standard deviation increase above the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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: No additional acute-duration studies of 1,3-DCB were located.

The NOAEL/LOAEL approach to MRL derivation results in same MRL as the 0.4 mg/kg/day value derived using the benchmark dose approach. Using the 37 mg/kg/day NOAEL for increased liver weight and the uncertainty factor of 100, the NOAEL/LOAEL approach yields an MRL of 0.4 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichlorobenzene (1,3-DCB)
CAS Numbers: 541-73-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 7
Species: Rat

Minimal Risk Level: [0.02] mg/kg/day [ ] ppm

Reference: McCauley PT, Robinson M, Daniel FB, et al. 1995. Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem Toxicol 18(2 & 3):201-221.

Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were administered 1,3-DCB in gavage doses of 0, 9, 37, 147, or 588 mg/kg/day in corn oil for 90 consecutive days (McCauley et al. 1995). End points evaluated during the study included clinical signs and mortality, body weight, and food and water consumption. At end of the exposure period, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads), and gross pathology was assessed. Histological examinations were performed on all tissues that were examined grossly in all high-dose rats and in one-half of control rats, as well as in the liver, thyroid, and pituitary glands from all animals in the 9, 37, and 147 mg/kg/day dose groups. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

Effects noted in study and corresponding doses: No compound-related deaths or overt clinical signs were observed. Body weight was reduced in both sexes at 588 mg/kg/day (24 and 10% lower than controls in males and females, respectively). The decreased weight gain was progressive throughout the exposure period and occurred despite increased food and water consumption in the same groups. Other effects included increased relative kidney weight in males at ≥147 mg/kg/day and in females at 588 mg/kg/day, but there were no renal histopathological changes in any of the exposed animals. Hematological alterations consisted of significant increases in leukocyte levels in males at 147 mg/kg/day and in females at 588 mg/kg/day, and erythrocyte levels in males at 588 mg/kg/day. Histopathology and serum chemistry findings indicated that the thyroid, pituitary, and liver were the most sensitive targets of toxicity, as discussed below. The lowest LOAEL is 9 mg/kg/day, which is the lowest tested dose and a minimal LOAEL for thyroid and liver effects.

Thyroid effects included significantly ($p \leq 0.05$) increased incidences of reduced colloidal density in follicles that exceeded normal variability in male rats at ≥9 mg/kg/day and in female rats at ≥37 mg/kg/day (control to high dose group incidences of 2/10, 8/10, 10/10, 8/9, and 8/8 in males, and 1/10, 5/10, 8/10, 8/10, and 8/9 in females). Depletion of colloid density in the thyroid was characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar. The severity of the colloid density depletion generally ranged from mild to moderate, increased with dose level, and was greater in males than females. Incidences of male rats with thyroid colloidal density depletion of moderate or marked severity were significantly increased at ≥147 mg/kg/day (0/10, 0/10, 2/10, 5/9, and 6/8). The 9 mg/kg/day dose is considered to be a minimal LOAEL for thyroid effects

because the morphological alterations (reduced colloidal density in follicles) are unlikely to be associated with functional changes in the thyroid.

Pituitary effects included significantly ($p \leq 0.05$) increased incidences of cytoplasmic vacuolization in the pars distalis in male rats at ≥147 mg/kg/day (2/10, 6/10, 6/10, 10/10, 7/7). The vacuoles were variably sized, irregularly shaped, and often poorly defined, and the severity of the lesions (i.e., number of cells containing vacuoles) ranged from minimal to mild and generally increased with increasing dose level. Incidences of male rats with pituitary cytoplasmic vacuolization of moderate or marked severity were significantly increased at 588 mg/kg/day (1/10, 0/10, 2/10, 3/9, and 7/7). The pituitary lesion was reported to be similar to "castration cells" found in gonadectomized rats and considered to be an indicator of gonadal deficiency. No compound-related pituitary lesions were observed in female rats. Serum cholesterol was significantly increased in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day in a dose-related manner, and serum calcium was significantly increased in both sexes at ≥37 mg/kg/day. The investigators suggested that these serum chemistry changes might reflect a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs. Based on the increased incidences of cytoplasmic vacuolation, the LOAEL for pituitary effects is 147 mg/kg/day.

Hepatic effects occurred in both sexes at 147 and 588 mg/kg/day, including significantly increased relative liver weight and incidences of liver lesions. Absolute organ weights were not reported. Liver lesions were characterized by inflammation, hepatocellular alterations (eosinophilic homogeneous inclusions), and hepatocellular necrosis. Liver lesions that were significantly ($p \leq 0.05$) increased included hepatocellular cytoplasmic alterations of minimal to mild severity in males at ≥147 mg/kg/day (1/10, 2/10, 1/10, 6/10, 7/9) and in females at 588 mg/kg/day (0/10, 2/10, 0/10, 1/10, 7/9), and necrotic hepatocyte foci of minimal severity at 588 mg/kg/day in both males (1/10, 2/10, 1/10, 2/10, 5/9) and females (0/10, 0/10, 0/10, 3/10, 5/9). Other statistically significant liver-associated effects included significantly increased serum AST levels (90–100% higher than controls) in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day. Serum cholesterol levels were significantly increased in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day, but might be pituitary-related, as indicated above. Serum LDH levels were reduced in males at ≥9 mg/kg/day and BUN levels were reduced in both sexes at 588 mg/kg/day, but the biological significance of decreases in these indices is unclear. The 9 mg/kg/day dose is considered to be a minimal LOAEL for liver effects because the main effect, increased serum AST, showed no clear dose-response and was only accompanied by necrotic liver lesions at a much higher dose (588 mg/kg/day).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{10}$ of 2.1 mg/kg/day for increased incidences of pituitary lesions is used as the basis for the MRL.

Benchmark dose analysis was conducted using the thyroid and pituitary lesion incidence data and serum AST and cholesterol levels summarized in Table A-17.

Table A-17. Thyroid, Pituitary and Liver Effects in Rats Orally Exposed to 1,3-Dichlorobenzene for 90 Days

Effect	Sex	Dose (mg/kg/day)				
		0	9	37	147	588
Thyroid, reduced follicular colloidal density	M	2/10	8/10[a]	10/10[a]	8/9[a]	8/8[a]
Pituitary, cytoplasmic vacuolation in pars distalis	M	2/10	6/10	6/10	10/10[a]	7/7[a]
Serum AST (U/L) (mean ± SD)	M	43.7 ± 37.7 (n=10)	87.6 ± 24.7[a] (n=10)	109.8 ± 9.5 (n=10)	88.0 ± 23.3[a] (n=10)	82.8 ± 13.8[a] (n=8)
Serum cholesterol (mg/dL) (mean ± SD)	M	73.5 ± 1.4 (n=10)	96.6 ± 1.7[a] (n=10)	111.1 ± 1.6[a] (n=10)	157.9 ± 2.5[a] (n=10)	89.5 ± 1.5[a] (n=8)
Serum cholesterol (mg/dL) (mean ± SD)	F	68.2 ± 1.7 (n=10)	85.0 ± 3.0 (n=10)	108.4 ± 2.2[a] (n=10)	158.9 ± 1.8[a] (n=10)	152.6 ± 2.6[a] (n=9)

[a]Significantly ($p \leq 0.05$) different from control

Source: McCauley et al. 1995

Continuous variable models (linear, polynomial, power, and Hill) in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the serum AST levels in the male rats and the serum cholesterol levels in the male and female rats. One standard deviation change from the control mean was selected as the BMR for each data set in the absence of a biological rationale for an alternative BMR. Initial modeling results using constant variance indicated that modeling should be performed using non-homogeneous variance. However, modeling results using non-homogeneous variance for each of the continuous variable models resulted in inadequate mean fit to the serum AST and cholesterol data, as indicated by p-values <0.0001 for mean fit.

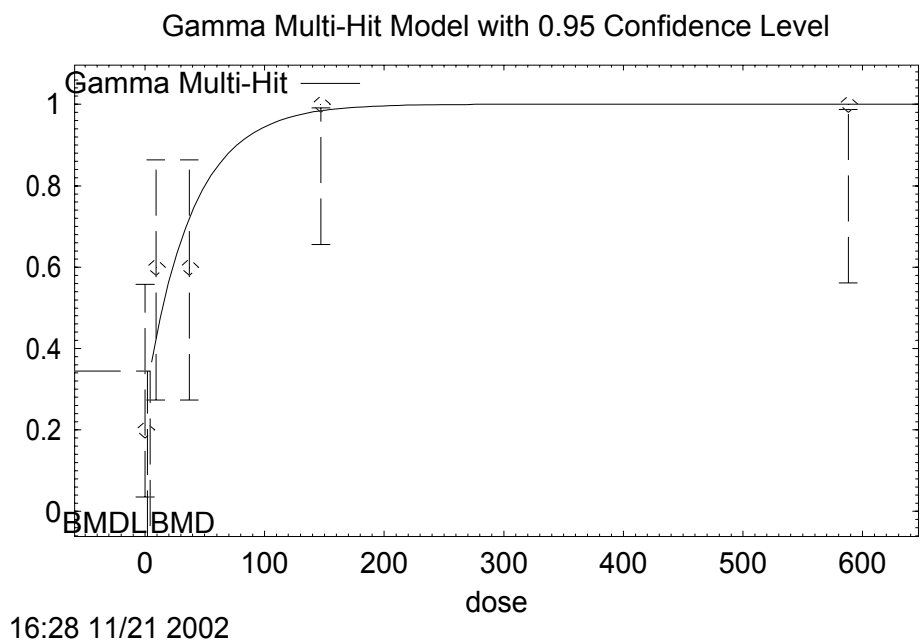
Dichotomous variable models available in the EPA Benchmark Dose Software were fit to the male rat incidence data for: (1) reduced follicular colloidal density in the thyroid, and (2) cytoplasmic vacuolation in the pars distalis of the pituitary. For each variable, AIC was used to select the best-fitting model from which BMDs and BMDLs were calculated, using a BMR of 10% extra risk. For the thyroid incidence data, none of the available dichotomous variable models provided adequate fit as indicated by chi-square goodness of fit p-values ≤0.002. For the pituitary cytoplasmic vacuolation incidence data, all of the models provided adequate fit as indicated by chi-square goodness of fit p-values >0.1 (Table A-18). The probit model provided the lowest AIC (43.442). However, a nearly identical AIC value (43.467) was provided by each of three other models (gamma, quantal-linear, and Weibull). Because the BMD_{10} of 4.08 mg/kg/day and associated $BMDL_{10}$ of 2.10 mg/kg/day from the gamma, quantal-linear, and Weibull models are lower than those from the probit model (BMD_{10} = 7.79 mg/kg/day; $BMDL_{10}$ = 4.46 mg/kg/day), a conservative health protective approach was taken and the lower $BMDL_{10}$ of 2.10 mg/kg/day was selected as the point of departure for deriving the MRL (Table A-18, Figure A-7). The $BMDL_{10}$ of 2.1 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability) to derive an MRL of 0.02 mg/kg/day.

Table A-18. BMD Modeling Results of Incidence Data for Pituitary Lesions in Male Rats Exposed to 1,3-Dichlorobenzene for 90 Days

Model	Chi-square p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Probit	0.4823	43.442	7.79	4.46
Gamma[b]	0.4887	43.467	4.08	2.1
Quantal-linear	0.4887	43.467	4.08	2.1
Weibull[b]	0.4887	43.467	4.08	2.1
Logistic	0.4639	43.58	7.49	4.29
Quantal-quadratic	0.376	44.122	17.11	10.10
Log-probit[c]	0.3154	44.674	7.33	3.29
Multi-stage[d]	0.3061	45.350	5.21	2.28
Log-logistic[c]	0.2190	46.518	2.34	0.66

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas ≥0; Degree of polynomial=2

Figure A-7. Observed Incidences for Pituitary Lesions in Male Rats and Incidences Predicted by the Gamma Model*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 10% extra risk. The gamma model plot in this figure is identical to plots produced by the quantal-linear and Weibull models.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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: No additional intermediate-duration studies of 1,3-DCB were located.

The NOAEL/LOAEL approach to MRL derivation provides support to the MRL of 0.02 mg/kg/day based on the BMD analysis of pituitary lesions. The lowest tested dose of 9 mg/kg/day is considered a minimal LOAEL for thyroid lesions and increases in serum AST. Using the minimal LOAEL of 9 mg/kg/day and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), the NOAEL/LOAEL approach yields an MRL of 0.03 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 44
Species: Dog

Minimal Risk Level: [0.07] mg/kg/day [ ] ppm

References: Naylor MW, Stout LD. 1996. One year study of p-dichlorobenzene administered orally via capsule to beagle dogs. Environmental Health Laboratory, Monsanto Company, St. Louis, MO. Study No. ML-94-210, March 25, 1996. MRID# 43988802. Unpublished.

EPA. 1996b. Data Evaluation Record (DER) for p-dichlorobenzene – chronic oral toxicity in dogs (MRID# 439888-01 and -02) for Section 6 (a) (2) and reregistration need. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances.

Experimental design: Groups of five male and five female beagle dogs were orally administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day for 1 year. Based on the summarized design of a 4-week dose range-finding study, it is presumed that dosing was 5 days/week. The 75 mg/kg/day dose is a time-weighted average level reflecting dose decreases at the beginning of the study in response to unexpected severe toxicity. An initial high dose of 150 mg/kg/day was adjusted to 100 mg/kg/day for males during week 3, and a further decrease to 75 mg/kg/day was made for both sexes at the beginning of week 6. Both high dose males and females were untreated during weeks 4 and 5 to allow for recovery. End points evaluated throughout the study included clinical observations (daily), body weight (weekly), and food consumption (weekly). Ophthalmoscopic examinations were performed prior to study start and just prior to study completion. Hematology (11 indices, including activated partial thromboplastin time), clinical chemistry (18 indices, including ALT, AST, GGTP, AP, and creatinine phosphokinase), and urinalysis (10 indices) were performed at month 6 and study completion. Organ weights, gross pathology, and histology were evaluated at study completion.

Effects noted in study and corresponding doses: Mortality occurred the first 25 days of the study before dose reduction; exposure to 150 mg/kg/day caused one male dog to be sacrificed in extremis on day 12, one male death on day 25, and one female death on day 24. A control male died on day 83, but all other dogs survived to the end of the study. Treatment-related clinical signs were primarily limited to severely affected high-dose dogs and the control male that died; these included hypoactivity, dehydration, decreased defecation, blood-like fecal color, emesis, emaciation, and/or pale oral mucosa. There were no significant group differences in mean body weight at the end of the study. Body weight gain was significantly reduced during the first month of the study, but recovered following dose reduction and adjustment of food availability. A mild anemia was observed at month 6 (significantly reduced red blood cells in females and HCT in males) at 75 mg/kg/day, but resolved by the end of the study. The mild anemia correlated with histologic findings of bone marrow erythroid hyperplasia in females, and splenic excessive hematopoiesis and megakaryocyte proliferation in both sexes, indicating a compensatory response to the earlier anemia. Hepatic effects occurred after 6 and 12 months at ≥50 mg/kg/day in both sexes as shown by changes in liver enzymes, increased liver weight, and/or histopathology. Effects on serum enzyme levels included significantly increased AP in males at 50 mg/kg/day at months 6 and 12 (731 and 620% higher than controls, respectively), females at 50 mg/kg/day at months 6 and

12 (525 and 330% higher), and females at 75 mg/kg/day at months 6 and 12 months (761 and 680% higher). Serum AP levels were not statistically significantly increased in the 75 mg/kg/day males at months 6 or 12, but only 3 animals were evaluated in this dose group. Other clinical chemistry findings included significantly increased ALT in females at 75 mg/kg/day at month 12 (253% higher than controls), increased GGTP in females at 75 mg/kg/day at months 6 and 12 (131 and 161% higher), and decreased albumin in males at 50 and 75 mg/kg/day at month 6 (16 and 18% lower than controls) and females at 75 mg/kg/day at month 6 (19% lower). Absolute and relative liver weights were significantly increased (40–70% higher than controls) in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatic lesions included hepatocellular hypertrophy (diffuse or multifocal in all males and females at 50 and 75 mg/kg/day and one female at 10 mg/kg/day), hepatocellular pigment deposition (two males and one female each at 50 and 75 mg/kg/day), bile duct/ductule hyperplasia (one male and one female at 75 mg/kg/day), and hepatic portal inflammation (periportal accumulation of neutrophils in one male at 50 mg/kg/day and two males at 75 mg/kg/day). Kidney effects included collecting duct epithelial vacuolation in one male at 75 mg/kg/day and at all dose levels in females (one each at 10 and 50 mg/kg/day and two at 75 mg/kg/day). The renal lesion was considered to be a possible effect of treatment at ≥50 mg/kg/day, because it was accompanied by increased relative kidney weight in females at ≥50 mg/kg/day and grossly observed renal discoloration in two females at 75 mg/kg/day.

The highest NOAEL and lowest LOAEL are 10 and 50 mg/kg/day, respectively, based on the increases in serum AP at 6 months. This serum enzyme change is a sufficient indication of intermediate-duration hepatotoxicity because the increases were similar in magnitude to those that were observed after 1 year and associated with increased liver weight and liver lesions; the latter effects likely developed earlier in the study but could not be detected due to the lack of organ weight and histology examinations at 6 months.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 10 mg/kg/day for increased serum AP is used as the basis for the MRL.

BMD analysis was conducted using the Naylor and Stout (1996) data for changes in serum AP in female dogs administered 1,4-DCB orally for 6 months, as shown in Table A-19. A BMR of 1 standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. Mean serum AP levels in the female dogs exhibited a dose-response relationship and were significantly higher in the 50 and 75 mg/kg/day groups, relative to controls. Although significantly increased mean serum AP levels were noted in the 50 mg/kg/day male dogs, the increase was not significant in the 75 mg/kg/day males; only three males in this dose group were available for the assessment of serum AP levels. Therefore, the male serum AP data were not modeled. The simplest model (linear) for continuous data from the EPA Benchmark Dose Software (Version 1.3.2) was initially fit to the female serum AP data; constant variance was selected. As shown in Table A-20, the linear model output indicated inadequate fit for constant variance (as indicated by a p-value <0.01 for the test of constant variance) and a model run using nonhomogeneous variance was suggested. However, using nonhomogeneous variance, inadequate model mean fit was obtained (p-value <0.01 for model mean fit) (see Table A-20). The more complex (polynomial, power, Hill) models were also fit to the serum AP data. The Hill model provided inadequate mean fit due to an insufficient number of dose groups (4, including controls), which resulted in insufficient (0) degrees of freedom. Both the polynomial and power models provided adequate mean fit (Table A-20). Following conventional protocol for selection of the point of departure (the adequate model with the lowest AIC [Akaike's Information Criteria]), the

$BMDL_{1sd}$ of 9.97 mg/kg/day (lower 95% confidence limit on the BMD_{1sd} of 12.48 mg/kg/day) was selected as the point of departure for deriving an intermediate-duration oral MRL for 1,4-DCB (see Table A-20, Figure A-8). The $BMDL_{1sd}$ of 9.97 mg/kg/day was duration-adjusted to 7 mg/kg/day and divided by an uncertainty factor of 100 to derive an MRL of 0.07 mg/kg/day.

Table A-19. Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 6 Months

Dose (mg/kg/day)	Group size	Mean serum AP level in IU/L (percent of control mean)
0	5	175.80 ± 50.05[a] --
10	5	176.00 ± 64.50 (100)
50	5	1098.20[b] ± 425.85 (625)
75	4	1513.50[c] ± 855.31 (861)

[a]Standard deviation
[b]Significantly different (p<0.01) from control group
[c]Significantly different (p<0.05) from control group

Source: Naylor and Stout 1996

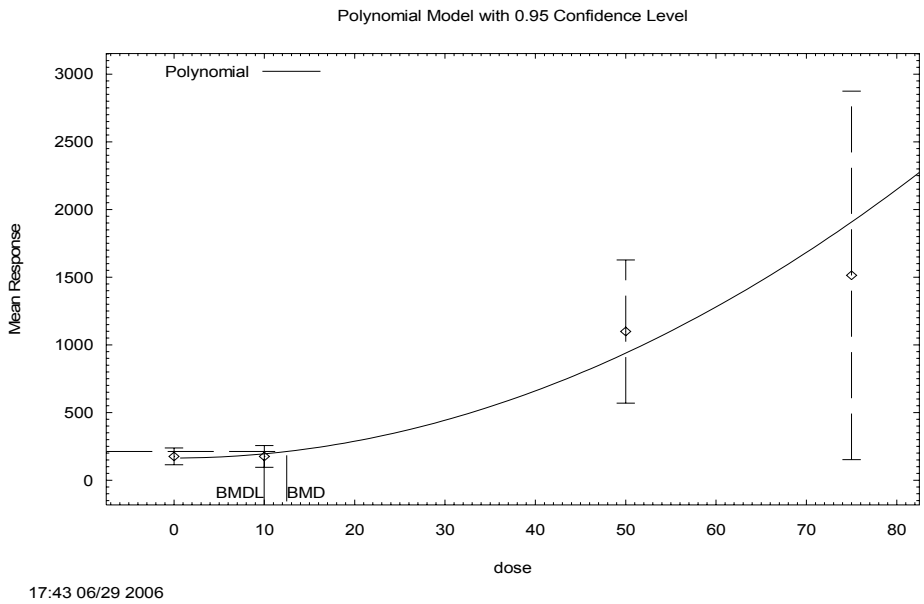
Table A-20. Model Predictions for Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 6 Months

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Linear[b,c]	<0.01	NA	NA	NA	NA
Linear[c,d]	NA	<0.01	NA	NA	NA
2-Degree polynomial[c,d]	**0.776**	**0.13**	**220.61**	**12.48**	**9.97**
Power[d]	0.774	0.14	222.59	12.00	6.62

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonhomogeneous variance assumed

BMD_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation above the control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}; NA = not applicable because model failed a goodness-of-fit test

Figure A-8. Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 6 Months*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 1 standard deviation above the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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? The $BMDL_{1sd}$ of 10 mg/kg/day was adjusted to a continuous exposure scenario as follows:

$$BMDL_{1sd\ ADJ} = (BMDL_{1sd})\ (5\text{days}/7\text{ days})$$
$$= (10\text{ mg/kg/day})\ (5\text{ days}/7\text{ days})$$
$$= 7\text{ mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL: The NOAEL/LOAEL approach to MRL derivation results in the same intermediate-duration oral MRL value as the benchmark dose approach. Using the NOAEL of 10 mg/kg/day for increased serum AP in dogs (Naylor and Stout 1996), the NOAEL is duration-adjusted to 7 mg/kg/day (10 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.07 mg/kg/day.

Information on the systemic toxicity of intermediate-duration oral exposure to 1,4-DCB is available from a number of studies conducted in rodents, mainly rats and mice, as well as the MRL study in dogs. Liver

and kidney effects are the most consistently observed, best characterized, and most sensitive findings in these studies. The lowest observed adverse effect level is for liver toxicity in dogs, although reproductive and developmental studies in rats indicate that offspring are particularly sensitive to 1,4-DCB toxicity during the postnatal pre-weaning period.

Hepatic effects induced by intermediate-duration oral exposures to 1,4-DCB ranged from increased liver weight and hepatocyte enlargement to hepatocellular degeneration, lesions, necrosis, and tumors in rats, mice, rabbits, and dogs. Increases in serum levels of enzymes and alterations in other end points (e.g., serum cholesterol and triglycerides) indicative of hepatocellular damage or liver dysfunction have also been induced. Increased liver weight is the most sensitive hepatic end point in subchronic studies in rats, observed at doses as low as 150 mg/kg/day for 4–13 weeks and 188 mg/kg/day for 192 days (Hollingsworth et al. 1956; Lake et al. 1997; Umemura et al. 1998). There was no indication of early liver damage in rats exposed to 150 mg/kg/day for 4 weeks using an immunohistochemical marker of centrilobular hepatocyte injury (Umemura et al. 1998), and increases in liver porphyrins in rats exposed to 50–200 mg/kg/day for 120 days were not considered to be toxicologically significant (Carlson 1977). Hepatocellular hypertrophy and decreased serum triglycerides occurred in rats exposed to ≥300 mg/kg/day for 13 weeks (NTP 1987; Lake et al. 1997). Higher dose levels of 1,4-DCB induced degenerative liver lesions in rats exposed to 376 mg/kg/day for 192 days (slight cirrhosis and focal necrosis) (Hollingsworth et al. 1956) or 1,200 mg/kg/day for 13 weeks (hepatocyte degeneration and necrosis) (NTP 1987). In mice, hepatocellular degeneration was induced at doses ≥600 mg/kg/day for 13 weeks (NTP 1987), and rabbits had cloudy swelling and minimal focal necrosis in the liver after exposure to 500 mg/kg/day for 367 days (Hollingsworth et al. 1956). Dogs are more sensitive to hepatic effects of 1,4-DCB than the other species based on increases in serum enzymes following exposure to doses as low as 50 mg/kg/day for 6 months in the MRL study (Naylor and Stout 1996).

Kidney effects, including collecting duct epithelial vacuolation, are additional effects of 1,4-DCB in the dogs exposed to ≥50 mg/kg/day for 1 year in the MRL study (Naylor and Stout 1996). Renal changes, including hyaline droplet accumulation, increased kidney weights, and tubular lesions, are characteristically observed effects of subchronic and chronic oral exposure to 1,4-DCB in male rats at doses ≥75 mg/kg/day (Bomhard et al. 1988; Lake et al. 1997; NTP 1987). These findings were not considered for MRL derivation because there is a scientific consensus that they are related to the α2μ-globulin nephropathy syndrome, which is specific to male rats and not relevant to humans. Subchronic studies in female rats found increased kidney weight, but no indications of nephrotoxic action (i.e., no histopathology or effects on urinary indices of renal function), following exposure to ≥188 mg/kg/day for 192 days or 600 mg/kg/day for 13 weeks (Bomhard et al. 1988; Hollingsworth et al. 1956).

Developmental toxicity studies provide no indications that 1,4-DCB is teratogenic in rats at oral doses as high as 1,000 mg/kg/day during gestation, although fetotoxicity occurred at maternally toxic levels ≥500 mg/kg/day (Giavini et al. 1986; Ruddick et al. 1983). Decreased maternal weight gain and increased incidences of extra ribs, a skeletal variation attributable to the maternal toxicity, occurred in rats at gestational dose levels ≥500 mg/kg/day, but not at 250 mg/kg/day (Giavini et al. 1986). In a 2-generation study, reproductive and developmental toxicity were evaluated in male and female rats that were orally exposed to 30, 90, or 270 mg/kg/day of 1,4-DCB (Bornatowicz et al. 1994). No effects on mating and fertility indices were observed at any level, although toxicity occurred in the offspring at doses ≥90 mg/kg/day. Effects at ≥90 mg/kg/day included reduced birth weight in F_1 pups and increased total number of deaths from birth to postnatal day 4 in F_1 and F_2 pups, clinical manifestations of dry and scaly skin (until approximately postnatal day 7) and tail constriction with occasional partial tail loss (during postnatal days 4–21) in F_1 and F_2 pups, reduced neurobehavioral performance (draw-up reflex evaluated at weaning) in F_2 pups, and increased relative liver weight in adult F_1 males. No exposure-

related changes were found at 30 mg/kg/day, indicating that this is the NOAEL for reproductive and developmental toxicity in rats.

As indicated above, liver, kidney, and perinatal developmental toxicity are main effects of concern for intermediate-duration oral exposure to 1,4-DCB in animals. The dog is the most sensitive tested species, as liver effects were induced by exposure to doses as low as 50 mg/kg/day for 6 months (Naylor and Stout 1996), which are below subchronic LOAELs of approximately 150–200 mg/kg/day for liver and kidney effects in rats and mice. The two-generation study in rats demonstrates that oral exposure to 1,4-DCB can cause perinatal developmental toxicity, including reduced birth weight and neonatal survival in F_1 and F_2 pups, at doses $\geq$90 mg/kg/day (Bornatowicz et al. 1994). Although this finding indicates that perinatal developmental toxicity is an additional sensitive end point for 1,4-DCB exposure, the hepatotoxicity induced in dogs at the 50 mg/kg/day dose level (Naylor and Stout 1996) is a more appropriate basis for MRL derivation.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Dog

Minimal Risk Level: [0.07] mg/kg/day [ ] ppm

References: Naylor MW, Stout LD. 1996. One year study of p-dichlorobenzene administered orally via capsule to beagle dogs. Environmental Health Laboratory, Monsanto Company, St. Louis, MO. Study No. ML-94-210, March 25, 1996. MRID# 43988802. Unpublished.

EPA. 1996b. Data Evaluation Record (DER) for p-dichlorobenzene – chronic oral toxicity in dogs (MRID# 439888-01 and -02) for Section 6 (a) (2) and reregistration need. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances.

Experimental design: Groups of five male and five female beagle dogs were orally administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day for 1 year. Based on the summarized design of a 4-week dose range-finding study, it is presumed that dosing was 5 days/week. The 75 mg/kg/day dose is a time-weighted average level reflecting dose decreases at the beginning of the study in response to unexpected severe toxicity. An initial high dose of 150 mg/kg/day was adjusted to 100 mg/kg/day for males during week 3, and a further decrease to 75 mg/kg/day was made for both sexes at the beginning of week 6. Both high-dose males and females were untreated during weeks 4 and 5 to allow for recovery. End points evaluated throughout the study included clinical observations (daily), body weight (weekly), and food consumption (weekly). Ophthalmoscopic examinations were performed prior to study start and just prior to study completion. Hematology (11 indices, including activated partial thromboplastin time), clinical chemistry (18 indices, including ALT, AST, GGTP, AP, and creatinine phosphokinase), and urinalysis (10 indices) were performed at month 6 and study completion (month 12). Organ weights, gross pathology, and histology were evaluated at month 12.

Effects noted in study and corresponding doses: Mortality occurred the first 25 days of the study before dose reduction; exposure to 150 mg/kg/day caused one male dog to be sacrificed in extremis on day 12, one male death on day 25, and one female death on day 24. A control male died on day 83, but all other dogs survived to the end of the study. Treatment-related clinical signs were primarily limited to severely affected high-dose dogs and the control male that died; these included hypoactivity, dehydration, decreased defecation, blood-like fecal color, emesis, emaciation, and/or pale oral mucosa. There were no significant group differences in mean body weight at the end of the study. Body weight gain was significantly reduced during the first month of the study, but recovered following dose reduction and adjustment of food availability. A mild anemia was observed at month 6 (significantly reduced red blood cells in females and HCT in males) at 75 mg/kg/day, but resolved by the end of the study. The mild anemia correlated with histologic findings of bone marrow erythroid hyperplasia in females, and splenic excessive hematopoiesis and megakaryocyte proliferation in both sexes, indicating a compensatory response to the earlier anemia. Hepatic effects occurred at ≥50 mg/kg/day in both sexes as shown by changes in liver enzymes, increased liver weight, and histopathology. Effects on serum enzyme levels included significantly increased AP in males at 50 mg/kg/day at months 6 and 12 (731 and 620% higher than controls, respectively), females at 50 mg/kg/day at months 6 and 12 (525 and 330% higher), and

females at 75 mg/kg/day at months 6 and 12 months (761 and 680% higher). Serum AP was also increased in males at 75 mg/kg/day after 6 and 12 months, but the changes were not statistically significant, possibly due to a reduced group size of 3 males at 75 mg/kg/day. Other clinical chemistry findings included significantly increased ALT in females at 75 mg/kg/day at month 12 (253% higher than controls), increased GGTP in females at 75 mg/kg/day at months 6 and 12 (131 and 161% higher), and decreased albumin in males at 50 and 75 mg/kg/day at month 6 (16 and 18% lower than controls) and females at 75 mg/kg/day at month 6 (19% lower). Absolute and relative liver weights were significantly increased (40-70% higher than controls) in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatocellular hypertrophy (diffuse or multifocal) occurred in all males and females at 50 and 75 mg/kg/day and in one female at 10 mg/kg/day. The study authors (Naylor and Stout 1996) considered the hepatocellular hypertrophy (multifocal) in the single 10 mg/kg/day female dog to be an adaptive response to a xenobiotic agent rather than a direct treatment-related effect. Other liver lesions considered to be treatment-related included hepatocellular pigment deposition (two males and one female each at 50 and 75 mg/kg/day), bile duct/ductule hyperplasia (one male and one female at 75 mg/kg/day), and hepatic portal inflammation (periportal accumulation of neutrophils in one male at 50 mg/kg/day and two males at 75 mg/kg/day). Kidney effects included collecting duct epithelial vacuolation in one male at 75 mg/kg/day and at all dose levels in females (one each at 10 and 50 mg/kg/day and two at 75 mg/kg/day). The renal lesion was considered to be a possible effect of treatment at ≥50 mg/kg/day, because it was accompanied by increased relative kidney weight in females at ≥50 mg/kg/day and grossly observed renal discoloration in two females at 75 mg/kg/day. The highest NOAEL and lowest LOAEL are 10 and 50 mg/kg/day, respectively, based on the hepatic effects (increased liver weight, changes in liver enzymes, and histopathology).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 10 mg/kg/day for increased serum AP is used as the basis for the MRL.

BMD analysis was performed on serum AP level and relative liver weight data for the female dogs exposed to 1,4-DCB for 1 year. The incidences of hepatocellular hypertrophy in the females (0/5, 1/5, 5/5, and 5/5 at 0, 10, 50, and 75 mg/kg/day) and males (0/5, 0/5, 5/5, and 5/5) are inappropriate for BMD modeling due to actual or effective responses of 0% in the control and low dose groups and 100% in the higher dose groups. The response in the low-dose female dog is effectively 0% because the authors implied that the hypertrophy in this single animal was not a hepatotoxic response. The incidences of the other liver lesions were not subjected to BMD analysis due to the low numbers of responders and group sizes. The data that were modeled are shown in Table A-21; the modeling results are shown in Table A-22.

Table A-21. Selected Liver Effects in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 12 Months

Dose (mg/kg/day)	Group size	Mean serum AP in IU/L (percent of control mean)	Mean relative liver weight in percent (percent of control mean)
0	5	173.40±55.09[a] --	2.71±0.17[a] --
10	5	181.80±69.22 (105)	3.05±0.83 (113)
50	5	745.80[c]±329.53 (430)	4.20[c]±0.47 (155)
75	4	1351.75[b]±652.46 (780)	4.61[c]±0.70 (170)

[a]Standard deviation
[b]Significantly different (p<0.05) from control group
[c]Significantly different (p<0.01) from control group

Source: Naylor and Stout 1996

Table A-22. Model Predictions for Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 12 Months

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{lsd} (mg/kg/day)	$BMDL_{lsd}$ (mg/kg/day)
Linear[b, c]	<0.01	0.42	NA	NA	NA
Linear[c, d]	0.94	<0.01	NA	NA	NA
2-Degree polynomial[c, d]	**0.94**	**0.65**	**215.12**	**15.40**	**12.32**
Power[d]	0.94	0.65	217.11	14.85	7.42

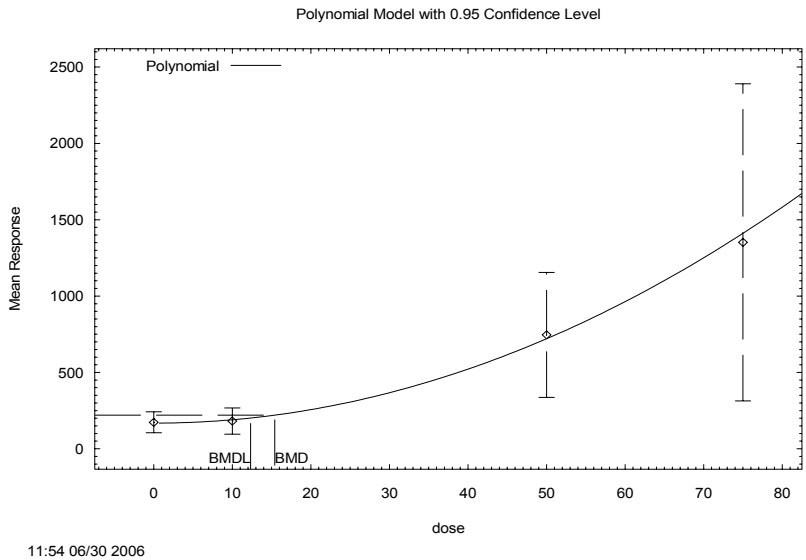
[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonhomogeneous variance assumed

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation above the control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}; NA = not applicable because model failed a goodness-of-fit test

For the relative liver weight data, the simplest continuous variable model (linear) from the EPA Benchmark Dose Software (Version 1.3.2) was initially fit; constant variance was assumed. A BMR of 1 standard deviation above the control mean was selected in the absence of a biological rationale for using an alternative BMR. The model output indicated that a non-homogeneous variance was more appropriate for the data set (as indicated by a p-value <0.01 for the test for constant variance). However, using non-homogeneous variance, inadequately modeled variance resulted (p-value <0.01). Similar inadequate results were obtained using the more complex polynomial and power models. The Hill model provided inadequate mean fit due to insufficient (0) degrees of freedom. Therefore, the relative liver weight data were judged to be unsuitable for benchmark dose analysis due to inadequate modeling of variance.

For the serum AP data, the simplest continuous variable model (linear) was initially fit; constant variance was assumed. A BMR of 1 standard deviation above the control mean was selected in the absence of a biological rationale for an alternative BMR. The model output indicated that a non-homogeneous variance was more appropriate for the data set (as indicated by a p-value <0.01 for the test for constant variance). However, using non-homogeneous variance, inadequate model mean fit was obtained (p-value <0.01). The more complex (polynomial, power, and Hill) models for continuous data were also fit to the serum AP data. The Hill model provided inadequate mean fit due to insufficient degrees (0) of freedom. Adequate mean fit was obtained with both the 2-degree polynomial and power models. Following conventional protocol for selection of the point of departure (the adequate model with the lowest AIC, the $BMDL_{1sd}$ of 12.32 mg/kg/day (lower 95% confidence limit on the BMD_{1sd} of 15.40 mg/kg/day) was selected as the point of departure for deriving the chronic-duration oral MRL (see Table A-22, Figure A-9). The $BMDL_{1sd}$ of 12.32 mg/kg/day was rounded to one significant figure (10 mg/kg/day), duration adjusted to 7 mg/kg/day, and divided by an uncertainty factor of 100 to derive an MRL of 0.07 mg/kg/day.

Figure A-9. Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 12 Months*



*BMD and BMDL (in mg/kg/day) are associated with 1 standard deviation above the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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? The $BMDL_{1sd}$ of 10 mg/kg/day was adjusted to a continuous exposure scenario as follows:

$$BMDL_{1sd\ ADJ} = (BMDL_{1sd})\ (5days/7\ days)$$
$$= (10\ mg/kg/day)\ (5/7)$$
$$= 7\ mg/kg/day$$

Other additional studies or pertinent information that lend support to this MRL: The NOAEL/LOAEL approach to MRL derivation results in the same chronic-duration oral MRL value as the benchmark dose approach. Using the NOAEL of 10 mg/kg/day for increased serum AP and other liver effects in dogs (Naylor and Stout 1996), the NOAEL is duration-adjusted to 7 mg/kg/day (10 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.07 mg/kg/day.

Additional information on the chronic oral effects of 1,4-DCB is available from one study each in rats, mice, and rabbits. Observed effects included nephropathy in rats (including tubular degeneration and atrophy in females) exposed to ≥150 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), hepatocellular degeneration and nephropathy in mice exposed to ≥300 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), and cloudy swelling and minimal focal necrosis in rabbits exposed to 500 mg/kg/day in 263 doses in 367 days (Hollingsworth et al. 1956). The lowest chronic LOAEL in these studies was 150 mg/kg/day for kidney effects in female rats (NTP 1987). Liver and kidney effects were induced in dogs in the principal study (Naylor and Stout 1996) at doses below the LOAELs in the other species.

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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

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

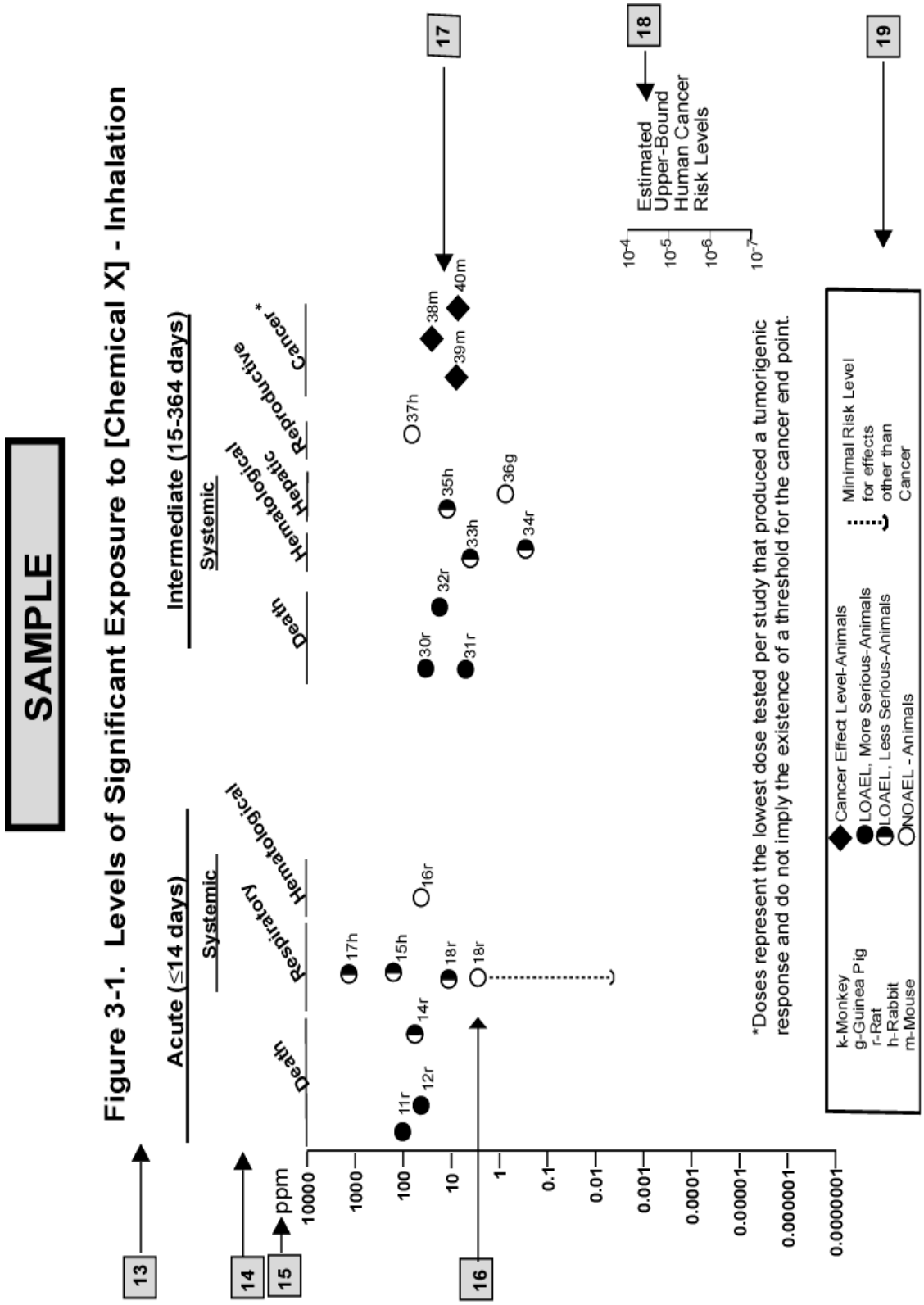
(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

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

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		
4 →								Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer						11	
							↓	
	38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).


SAMPLE
Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation
Acute (≤14 days)
Systemic
Respiratory
Hematological
Death
Intermediate (15-364 days)
Systemic
Hematological
Hepatic
Reproductive
Cancer *
Death
ppm
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
11r
12r
14r
17h
15h
18r
16r
18r
30r
31r
32r
33h
35h
34r
36g
37h
38m
39m
40m
Estimated Upper-Bound Human Cancer Risk Levels
10^{-4}
10^{-5}
10^{-6}
10^{-7}
*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
k-Monkey
g-Guinea Pig
r-Rat
h-Rabbit
m-Mouse
Cancer Effect Level-Animals
LOAEL, More Serious-Animals
LOAEL, Less Serious-Animals
NOAEL - Animals
Minimal Risk Level for effects other than Cancer
13
14
15
16
17
18
19

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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	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

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

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

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

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

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APPENDIX D. INDEX

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