TOXICOLOGICAL PROFILE FOR CHLORINATED DIBENZO-*p*-DIOXINS

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

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DISCLAIMER

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

UPDATE STATEMENT

A toxicological profile for chlorinated dibenzo-*p*-dioxins was released in February 1998. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and 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 being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but 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.

Each toxicological profile begins with a public health statement, which 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 protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

> (A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order 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.
>
> (C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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 the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are 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 Environmental Protection Agency (EPA). The availability of the revised priority list of the 275 hazardous substances was announced in the *Federal Register* on February 28, 1994 (59 FR 9486). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); and October 28, 1992 (57 FR 48801).

Section 104 (i) (3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-447-1544 (to be replaced by 1-888-42-ATSDR in 1999)
or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://atsdr1.atsdr.cdc.gov:8080

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

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure

history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

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

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. 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.

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

PEER REVIEW

A peer review panel was assembled for chlorinated dibenzo-*p*-dioxins. The panel consisted of the following members:

1. James Olson, Department of Pharmacology and Toxicology, State University of New York at Buffalo, Buffalo, NY;

2. John Ryan, Bureau of Chemical Safety, Health and Welfare Canada, Ottawa, Ontario, Canada; and

3. Arnold Schecter, College of Medicine, State University of New York, Health Science Center, Binghamton, NY.

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

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

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

PAST PEER-REVIEWS

Several drafts of the Toxicological Profile for Chlorinated Dibenzo-*p*-Dioxins were submitted for a peer-review in the past.

Draft 1997

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Draft 1994 (scientific panel meeting)

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chlorinated dibenzo-*p*-dioxins (CDDs) and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up. CDDs (all types) have been found in at least 126 of the 1,467 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for these substances. As more sites are evaluated, the number of sites with CDDs may increase. This is important because exposure to these substances may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You 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 CDDs, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE CDDs?

CDDs are a family of 75 different compounds commonly referred to as polychlorinated dioxins. These compounds have varying harmful effects. The CDD family is divided into eight groups of chemicals based on the number of chlorine atoms in the compound. The group with one chlorine atom is called the mono-chlorinated dioxin(s). The groups with two through eight chlorine atoms are called di-chlorinated dioxin (DCDD), tri-chlorinated dioxin (TrCDD), tetra-chlorinated dioxin (TCDD), penta-chlorinated dioxin (PeCDD), hexa-chlorinated dioxin (HxCDD), hepta-chlorinated dioxin (HpCDD), and octa-chlorinated dioxin (OCDD). The chlorine atoms can be attached to the dioxin molecule at any one of eight positions. The name of each CDD indicates both the number

and the positions of the chlorine atoms. For example, the CDD with four chlorine atoms at positions 2, 3, 7, and 8 on the dioxin molecule is called 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or 2,3,7,8-TCDD. 2,3,7,8-TCDD is one of the most toxic of the CDDs to mammals and has received the most attention. Thus, 2,3,7,8-TCDD serves as a prototype for the CDDs. CDDs with toxic properties similar to 2,3,7,8-TCDD are called "dioxin-like" compounds.

In the pure form, CDDs are colorless solids or crystals. CDDs enter the environment as mixtures containing a variety of individual components and impurities. In the environment they tend to be associated with ash, soil, or any surface with a high organic content, such as plant leaves. In air and water, a portion of the CDDs may be found in the vapor or dissolved state, depending on the amount of particulate matter, temperature, and other environmental factors. 2,3,7,8-TCDD is odorless. The odors of the other CDDs are not known. CDDs are known to occur naturally, and are also produced by human activities. They are naturally produced from the incomplete combustion of organic material by forest fires or volcanic activity. CDDs are not intentionally manufactured by industry, except in small amounts for research purposes. They are unintentionally produced by industrial, municipal, and domestic incineration and combustion processes. Currently, it is believed that CDD emissions associated with human incineration and combustion activities are the predominant environmental source.

CDDs (mainly 2,3,7,8-TCDD) may be formed during the chlorine bleaching process used by pulp and paper mills. CDDs occur as a contaminant in the manufacturing process of certain chlorinated organic chemicals, such as chlorinated phenols. 2,3,7,8-TCDD is a by-product formed during the manufacture of 2,4,5-trichlorophenol (2,4,5-TCP). 2,4,5-TCP was used to produce hexachlorophene (used to kill bacteria) and the herbicide, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Various formulations of 2,4,5-T have been used extensively for weed control on crops and range lands, and along roadways throughout the world. 2,4,5-T was a component of Agent Orange, which was used extensively by the U.S. military in the Vietnam War. In most industrialized countries the use of products contaminated with CDDs has been greatly reduced. Use of hexachlorophene and the herbicide 2,4,5-T is currently restricted in the United States. Other chlorinated chemicals, like pentachlorophenol (PCP), used to preserve wood, do contain some of the more highly chlorinated CDDs (those with more chlorine atoms), but 2,3,7,8-TCDD is not usually found. The use of PCP has been restricted to certain manufacturing applications.

Currently, CDDs are primarily released to the environment during combustion of fossil fuels (coal, oil, and natural gas) and wood, and during incineration processes (municipal and medical solid waste and hazardous waste incineration). While incineration may be the primary current source of release of CDDs into the environment, the levels of CDDs produced by incineration are extremely low. CDDs are associated with ash generated in combustion and incineration processes. Emissions from incinerator sources vary greatly and depend on management practices and applied technologies. CDDs also have been detected at low concentrations in cigarette smoke, home-heating systems, and exhaust from cars running on leaded gasoline or unleaded gasoline, and diesel fuel. Burning of many materials that may contain chlorine, such as plastics, wood treated with pentachlorophenol (PCP), pesticide-treated wastes, other polychlorinated chemicals (polychlorinated biphenyls or PCBs), and even bleached paper can produce CDDs.

Although this public health statement will focus on CDDs, it is important to note that CDDs are found in the environment together with other structurally related chlorinated chemicals, such as chlorinated dibenzofurans (CDFs) and polychlorinated biphenyls (PCBs). Therefore, people are generally exposed to mixtures of CDDs and other classes of toxicologically and structurally similar compounds. 2,3,7,8-TCDD is one of the most toxic and extensively studied of the CDDs and serves as a prototype for the toxicologically relevant or “dioxin-like CDDs. Based on results from animal studies, scientists have learned that they can express the toxicity of dioxin-like CDDs as a fraction of the toxicity attributed to 2,3,7,8-TCDD. For example, the toxicity of dioxin-like CDDs can be half or one tenth or any fraction of that of 2,3,7,8-TCDD. Scientists call that fraction a Toxic Equivalent Factor (TEF). More information on TEFs can be found in Section 2.5.

For more information on CDDs, please refer to Chapters 3, 4, and 5.

1.2 WHAT HAPPENS TO CDDs WHEN THEY ENTER THE ENVIRONMENT?

CDDs are released into the air in emissions from municipal solid waste and industrial incinerators. Exhaust from vehicles powered with leaded and unleaded gasoline and diesel fuel also release CDDs to the air. Other sources of CDDs in air include: emissions from oil- or coal-fired power plants, burning of chlorinated compounds such as PCBs, and cigarette smoke. CDDs formed during combustion processes are associated with small particles in the air, such as ash. The larger particles will be deposited close to the emission source, while very small particles may be

transported longer distances. Some of the lower chlorinated CDDs (DCDD, TrCDD, and some of the TCDDs) may vaporize from the particles (and soil or water surfaces) and be transported long distances in the atmosphere, even around the globe. It has been estimated that 20 to 60% of 2,3,7,8-TCDD in the air is in the vapor phase. Sunlight and atmospheric chemicals will break down a very small portion of the CDDs, but most CDDs will be deposited on land or water.

CDDs occur as a contaminant in the manufacture of various chlorinated pesticides and herbicides, and releases to the environment have occurred during the use of these chemicals. Because CDDs remain in the environment for a long time, contamination from past pesticide and herbicide use may still be of concern. In addition, improper storage or disposal of these pesticides and waste generated during their production can lead to CDD contamination of soil and water.

CDDs are released in waste waters from pulp and paper mills that use chlorine or chlorine-containing chemicals in the bleaching process. Some of the CDDs deposited on or near the water surface will be broken down by sunlight. A very small portion of the total CDDs in water will evaporate to air. Because CDDs do not dissolve easily in water, most of the CDDs in water will attach strongly to small particles of soil or organic matter and eventually settle to the bottom. CDDs may also attach to microscopic plants and animals (plankton) which are eaten by larger animals, that are in turn eaten by even larger animals. This is called a food chain. Concentrations of chemicals such as the most toxic, 2,3,7,8-chlorine substituted CDDs, which are difficult for the animals to break down, usually increase at each step in the food chain. This process, called biomagnification, is the reason why undetectable levels of CDDs in water can result in measurable concentrations in aquatic animals. The food chain is the main route by which CDD concentrations build up in larger fish, although some fish may accumulate CDDs by eating particles containing CDDs directly off the bottom.

CDDs deposited on land from combustion sources or from herbicide or pesticide applications bind strongly to the soil, and therefore are not likely to contaminate groundwater by moving deeper into the soil. However, the presence of other chemical pollutants in contaminated soils, such as those found at hazardous waste sites or associated with chemical spills (for example, oil spills), may dissolve CDDs, making it easier for CDDs to move through the soil. The movement of chemical waste containing CDDs through soil has resulted in contamination of groundwater. Soil erosion

and surface runoff can also transport CDDs into surface waters. A very small amount of CDDs at the soil surface will evaporate into air. Certain types of soil bacteria and fungus can break CDDs down, but the process is very slow. In fact, CDDs can exist in soil for many years. Plants take up only very small amounts of CDDs by their roots. Most of the CDDs found on the parts of plants above the ground probably come from air and dust and/or previous use of CDD-containing pesticides or herbicides. Animals (such as cattle) feeding on the plants may accumulate CDDs in their body tissues (meat) and milk.

For more information on what happens to CDDs in the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO CDDs?

CDDs are found at very low levels in the environment. These levels are measured in nanograms and picograms. One nanogram (ng) is one billionth of a gram, and one picogram (pg) is one trillionth of a gram. In some contaminated soils, concentrations of CDDs are reported as parts per billion. One part per billion (ppb) is one part CDD per billion parts of soil. The concentration of CDDs is often reported as parts per trillion, in samples of air, water, or soil. One part per trillion (ppt) is one part CDD per trillion parts of air, water, or soil. In some rural areas where CDD concentrations are very low in air or water, measurements are given in parts per quadrillion (ppq), which means one part CDD per quadrillion parts of air or water.

CDDs are found everywhere in the environment, and most people are exposed to very small background levels of CDDs when they breath air, consume food or milk, or have skin contact with materials contaminated with CDDs. For the general population, more than 90% of the daily intake of CDDs, CDFs, and other dioxin-like compounds comes from food, primarily meat, dairy products, and fish. CDDs may be present at much lower levels in fruits and vegetables. The actual intake of CDDs from food for any one person will depend on the amount and type of food consumed and the level of contamination. Higher levels may be found in foods from areas contaminated with chemicals, such as pesticides or herbicides, containing CDDs as impurities. CDDs have been measured in human milk, cow's milk, and infant formula, so infants are known to be exposed to CDDs.

Most surface water in the United States typically does not contain 2,3,7,8-TCDD and other CDDs at levels that are high enough to be measured (1 ppq or more). Municipal drinking water does not usually contain CDDs because the CDDs do not dissolve in water and primarily stick to particles, which are usually filtered out of treated drinking water. This means that using tap water to wash clothes or to bathe or shower, or swimming in pools or in uncontaminated lakes, rivers, or at ocean beaches will not expose people to significant levels of CDDs. Although CDDs are not usually found in filtered, treated drinking water, they have, on occasion, been detected in unfiltered groundwater from areas with known CDD contamination.

Exposure to CDDs can also occur through skin contact with chlorinated pesticides and herbicides, contaminated soils, or other materials such as PCP-treated wood and PCB transformer fluids. Background levels of CDDs in soil are higher than background levels in both air and water. Background levels of CDDs detected in uncontaminated soils in the United States are generally very low or not detectable. 2,3,7,8-TCDD is not usually found in rural soil, but is typically found in soil in industrialized areas at levels ranging from 0.001 to 0.01 ppb. However, higher levels of 2,3,7,8-TCDD may be found in areas where CDDs have contaminated the soil. For example, contaminated soil at Times Beach, Missouri, had levels of 2,3,7,8-TCDD ranging from 4.4–317 ppb.

If CDDs are present at all in outdoor air in rural areas, they are generally present at very low levels or at concentrations near the detection limits for testing equipment. In winter, because of the burning of wood and other fuels for home heating, CDD levels may be slightly higher than during other seasons. In general, the background air levels of CDDs in urban areas are higher than in rural areas. Typical levels of CDDs in outdoor air in urban areas and industrial areas averaged 2.3 picograms per meter cubed (pg/m^3). 2,3,7,8-TCDD is not usually found in rural or urban air, but it is found in air near urban waste incinerators and high-traffic areas. The air around people who are smoking cigarettes may also have CDDs at levels above background levels. Although breathing contaminated air is a minor route of exposure for most people, exposure may be greater in areas near these CDD sources.

CDDs have been found in all samples of adipose tissue and blood (serum lipids) from individuals with no known previous exposure. This indicates that all people are exposed to small amounts of CDDs. Levels of 2,3,7,8-TCDD in serum from the general population typically range from 3 to

7 ppt (on a lipid basis), and rarely exceed 10 ppt. Typically, lower levels of CDDs are found in less industrialized countries and in younger people.

The production, use, and disposal of pesticides and phenoxy herbicides, disposal of production waste containing 2,3,7,8-TCDD, industrial accidents involving 2,4,5-trichlorophenol (2,3,5-TCP), and the consumption of CDD-contaminated food, have all led to increased potential for excess exposure of some groups of people. 2,3,7,8-TCDD has been detected at 91 of the 126 hazardous waste sites on the NPL that have been reported to contain CDDs. People living around these sites may be exposed to above-background levels of 2,3,7,8-TCDD and other CDDs. Elevated levels of CDDs have been reported in fish, shellfish, birds, and mammals collected in areas surrounding various chemical production facilities, various hazardous waste sites, and pulp and paper mills using the chlorine bleaching process. Sometimes these findings have resulted in closure of these areas for the purpose of fishing. People who eat contaminated food from these contaminated areas are at risk of increased exposure to CDDs.

Occupational exposure to CDDs generally occurs through breathing contaminated air, or through skin contact with materials containing CDDs. Workers with the potential to be exposed to above-average levels of CDDs include those involved in the production or handling of certain chlorinated phenols (such as 2,4,5-TCP, PCP) or chlorinated pesticides or herbicides (such as 2,4,5-T, 2,4-D, hexachlorophene, Silvex®), and those involved in application of chlorinated pesticides containing CDDs as impurities. Workers whose jobs involve pressure treatment of wood with PCP and the handling of PCP-treated wood products, chlorination processes at pulp and paper mills, or operation of municipal solid waste or hazardous waste incinerators may have increased exposure to CDDs. Finally, workers involved in hazardous waste clean-up or clean-up of PCB transformer and/or capacitor fires including emergency service personnel like fire fighters and police who respond to such fires are also at additional risk of exposure to CDDs. Most of these occupational exposures have been significantly reduced in recent years.

In general, workers involved in the manufacture of 2,4,5-TCP and subsequent products were exposed to far greater levels of 2,3,7,8-TCDD than those involved in the handling and application of chlorinated pesticides containing CDDs. Current serum lipid levels of 2,3,7,8-TCDD in a small number of U.S. Air Force veterans who were directly involved in the aerial spraying of herbicides (Agent Orange contaminated with 2,3,7,8-TCDD) in Vietnam as part of Operation Ranch Hand,

are up to 3 times higher than the general population. However, while studies on blood or fatty tissue 2,3,7,8-TCDD levels in U.S. Army ground combat Vietnam veterans also found some individuals with 2,3,7,8-TCDD levels higher than those of the general population, overall, most Vietnam veterans and Vietnamese living in Vietnam studied to dated have blood and fatty tissue 2,3,7,8-TCDD levels comparable to members of the general U.S. population.

For more information on exposure to CDDs, see Chapter 5.

1.4 HOW CAN CDDs ENTER AND LEAVE MY BODY?

CDDs can enter your body when you breathe contaminated air, eat contaminated food, or have skin contact with contaminated soil or other materials. The most common way CDDs can enter your body is by eating food contaminated with CDDs.

If you breathe air that contains CDDs, the CDDs can enter your body through your lungs and pass into the blood stream, but we do not know how fast or how much of the CDDs will enter the blood stream. If you swallow food or water containing CDDs, most of the CDDs will enter your body and pass from the intestines to the blood stream. Smaller amounts of highly chlorinated CDDs will enter your body compared to the less chlorinated 2,3,7,8-TCDD. If you swallow soil containing CDDs, a small amount of the CDDs will pass through the intestines into the blood stream. If soil contaminated with CDDs comes into contact with your skin, some of the CDDs will enter the body but we do not know how fast they will enter the blood stream.

Once in your body, CDDs can be found in most tissues with the highest amounts found in the liver and body fat (adipose tissue). Body fat and possibly the liver can store CDDs for many years before eliminating them from the body. CDDs with chlorine atoms in the 2, 3, 7, and 8 positions and highly chlorinated dioxins, such as OCDD, are generally found in higher concentrations in the fat than other CDDs.

Little is known about CDDs breakdown in the human body. Studies in animals show that some of the 2,3,7,8-TCDD from food is slowly broken down. There is evidence from animals suggesting that the break-down products are less harmful than the unchanged 2,3,7,8-TCDD.

For people, the average time it takes to remove one-half of the 2,3,7,8-TCDD from the body is highly variable and may take from 7 to 12 years. There is less information on the other CDDs, but what information exists suggests 5 to 15 years. CDDs are eliminated from the body primarily in the stool, and only a small amount leaves the body in the urine. Some CDDs will leave the body in the breast milk of nursing mothers.

Much less is known about how much other CDD compounds will enter the body, how much will be stored in the body and for how long, and how they are removed from the body.
For more information about how CDDs can enter and leave your body, see Chapter 2.

1.5 HOW CAN CDDs AFFECT MY HEALTH?

Many studies have looked at how CDDs can affect human health. Most of these studies examined workers exposed during the manufacture of chemicals and pesticides contaminated with 2,3,7,8-TCDD. Other studies have looked at American Vietnam veterans and Vietnamese populations exposed to Agent Orange and populations exposed to 2,3,7,8-TCDD as a result of an accident. The workers and Vietnam veterans were most likely exposed to 2,3,7,8-TCDD mainly through breathing and skin contact. People who were accidentally exposed to 2,3,7,8-TCDD in Seveso, Italy, or Times Beach, Missouri, were probably exposed through eating and drinking contaminated food and milk, breathing contaminated particles and dust, through skin contact with contaminated soil and through unintentional hand-to mouth activity. Epidemiology is an inexact science and many of the human studies have many shortcomings which make it difficult for scientists to establish an association between 2,3,7,8-TCDD exposure levels and health effects. A common problem with most of the human studies is that the people are exposed to a number of chemicals at the same time. In most human health studies, we do not know how much 2,3,7,8-TCDD people were exposed to or how long the exposure lasted. In other studies, the people were examined many years after they were exposed and some of the effects may have not have been present at the time of examination or the effects observed may not have been caused by 2,3,7,8-TCDD. Some of the more recent studies have measured 2,3,7,8-TCDD levels in the blood or fat tissue of exposed populations. The levels of 2,3,7,8-TCDD in the blood or fat tissue can be used to estimate the extent of past exposures.

A number of effects have been observed in people exposed to 2,3,7,8-TCDD levels which are at least 10 times higher than background levels. The most obvious health effect in people exposed to relatively large amounts of 2,3,7,8-TCDD is chloracne. Chloracne is a severe skin disease characterized by acne-like lesions. Chloracne generally occurs on the face and upper body, but may occur elsewhere on the body. Unlike common acne, severe chloracne is harder to cure and can be more disfiguring. In milder cases, the lesions heal several months after exposure ends. In more severe cases, the lesions may last for many years after exposure. Most of the chloracne cases have been attributed to accidental exposure to high doses of 2,3,7,8-TCDD. Other effects to the skin, such as erythematous or red skin rashes, discoloration, and excessive body hair, have been reported to occur in people following exposure to high concentrations of 2,3,7,8-TCDD. Changes in blood and urine that may indicate liver damage have been observed in people. Alterations in the ability of the liver to metabolize (or breakdown) hemoglobin, lipids, sugar, and protein have been reported in people exposed to relatively high concentrations of 2,3,7,8-TCDD. Most of the effects are considered mild and were reversible. However, in some people these effects may last for many years. Slight increases in the risk of diabetes and abnormal glucose tolerance have been observed in some studies of people exposed to 2,3,7,8-TCDD. We do not have enough information to know if exposure to 2,3,7,8-TCDD will result in reproductive or developmental effects in people, but animal studies suggest that this is a potential health concern. Several studies of workers exposed to high levels (with body burdens more than 50 times higher than background body burden levels) of 2,3,7,8-TCDD suggest that exposure to 2,3,7,8-TCDD may increase the risk of cancer in people.

The Department of Health and Human Services (DHHS) has determined that it is reasonable to expect that 2,3,7,8-TCDD may cause cancer. The International Agency for Research on Cancer (IARC) has determined that 2,3,7,8-TCDD can cause cancer in people, but that it is not possible to classify other CDDs as to their carcinogenicity to humans. The EPA has determined that 2,3,7,8-TCDD is a probable human carcinogen when considered alone and when considered in association with phenoxy herbicides and/or chlorophenols. The EPA has determined also that a mixture of CDDs with six chlorine atoms (4 of the 6 chlorine atoms at the 2, 3, 7, and 8 positions) is a probable human carcinogen.

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

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

The health effects of some CDDs have been extensively studied in animals. Some CDDs are much more toxic than others. 2,3,7,8-TCDD and, to a lesser extent, CDDs with five (penta) or six (hexa) chlorine atoms substituted in the 2, 3, 7, and 8 positions, are extremely toxic to animals. Other CDDs, which do not have chlorine atoms substituted in the 2, 3, 7, and 8 positions, are considered relatively less toxic compared to 2,3,7,8-TCDD.

2,3,7,8-TCDD has been the most extensively studied CDD and it has been shown to cause a large number of adverse health effects in animals. There are always going to be some difficulties in using animal data to quantify health risks in people. In general, the doses used in the animal studies result in body burdens that are at least 10 times higher than human background body burdens, often the animal studies use doses that are over 1,000 times higher than human background levels. Some animal species are much more acutely sensitive to 2,3,7,8-TCDD than others. For example, it takes several thousand times more 2,3,7,8-TCDD to kill a hamster than a guinea pig. The reason for the difference in sensitivity among species is currently being investigated. For other effects, such as reproductive toxicity, there is very little difference in sensitivity between hamsters and guinea pigs. Another consideration in using animal data to predict health effects in people exposed to CDDs in the environment is the design of the animal studies. In most of the animal studies, the animals were exposed to only 2,3,7,8-TCDD, the most toxic CDD. 2,3,7,8-TCDD is rarely the main CDD found in the environment and people are typically exposed to a number of CDDs and compounds with similar toxic actions. Until scientists learn more about possible differences between people and animals, levels recommended to be of little or no risk to human health are based on the more sensitive species and the assumption that effects in animals could occur in people. This approach is further justified on the basis that humans are likely to exhibit a wide range of sensitivities to various health effects and the need to protect the most susceptible individuals.

In certain animal species, 2,3,7,8-TCDD is especially harmful and can cause death after a single exposure to small amounts. Before death, animals may lose as much as 40% or more of their body weight following a single dose of 2,3,7,8-TCDD. Exposure to non-lethal levels added in their food can cause a variety of adverse effects in animals, such as weight loss, biochemical and degenerative changes in the liver. Some animals that were exposed to CDDs in their food had effects to the skin such as hair loss, swelling of the face, and moderate to severe chloracne. In many species of animals, the immune system appears to be extremely sensitive to 2,3,7,8-TCDD. At relatively low levels (approximately 10 times higher than human background body burdens), 2,3,7,8-TCDD weakens the immune system and causes a decrease in the system's ability to fight foreign substances such as bacteria and viruses.

Exposure to 2,3,7,8-TCDD can cause reproductive damage and birth defects in animals. Decreases in fertility, altered levels of sex hormones, reduced production of sperm, and increased rates of miscarriages were found in animals exposed to 2,3,7,8-TCDD in food. Rats and mice that were exposed to small amounts of 2,3,7,8-TCDD in food for a long time developed cancer of the liver and thyroid, and other types of cancer.

The results of the oral animal studies suggest that the most sensitive effects (effects that will occur at the lowest doses) are immune, endocrine, and developmental effects. It is reasonable to assume that these will also be the most sensitive effects in humans.

We know less about the ability of other CDDs to cause adverse health effects. However, it appears that all CDDs with chlorine in the 2, 3, 7, and 8 positions have similar effects to 2,3,7,8-TCDD but the effects occur at higher doses.

Relatively large amounts of 2,3,7,8-TCDD applied to the skin of some animal species have resulted in deaths. Smaller amounts have resulted in weight loss, acne-like sores on the skin, and biochemical and degenerative changes in the liver. In addition, mice that had 2,3,7,8-TCDD repeatedly applied to their skin developed skin cancer. Although effects in animals following exposure through the skin have not been as extensively studied as effects following exposure in food, they appear to be quite similar. The ability of other CDDs to cause adverse health effects in animals following exposure to the skin has not been well studied.

You can find out more information on the health effects of CDDs in Chapter 2.

1.6 HOW CAN CDDs AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Very few studies have looked at how CDDs can affect children's health. Chloracne has been observed in children exposed to much higher than current background levels of 2,3,7,8-TCDD. The children appeared to be more sensitive (effects occurred at a lower body burden) than adults. We do not know why children are more sensitive than adults to this effect. It is likely that children exposed to higher than background levels will have similar effects as adults.

We do not know if exposure to CDDs will result in birth defects or other developmental effects in people. Birth defects have been observed in animals exposed to higher than background levels of 2,3,7,8-TCDD. The developing animal is very sensitive to 2,3,7,8-TCDD. In some studies, effects were observed at body burdens 10 times higher than human background body burden levels. Offspring of animals exposed to 2,3,7,8-TCDD in food during pregnancy often had severe birth defects including bleeding, skeletal deformities, kidney defects, weakened immune responses, impaired development of the reproductive system, and learning and behavioral impairments. Exposure to other CDDs, such as 2,7-DCDD, 1,2,3,7,8-PeCDD, OCDD, and HxCDD, can also result in developmental effects in animals.

We have no information to suggest that there are any differences between children and adults in terms of how much CDDs will enter the body, where CDDs can be found in the body, and how fast CDDs will leave the body. CDDs from the mother can enter her unborn baby through the placenta. It can also be transferred from the mother to infant through breast milk. Because CDDs have been measured in human milk, cows milk, and infant formula, nursing infants are also exposed to CDDs. In most cases the beneficial aspects (biological and psychological) of breast-feeding outweigh any risks from exposure to CDDs from mother's milk.

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

If your doctor finds that you have been exposed to significant amounts of CDDs, ask your doctor if children may also be exposed. When necessary your doctor may need to ask your state Department of Public Health to investigate.

Structural material used in building homes such as chemically treated lumber for decking and plastic PVC pipes used in water pipes and other conduits can release CDDS if they are burned as refuse during construction or if there is a structural fire in your home. To avoid exposures from some of these sources, construction refuse should not be burned near your home especially when children are out playing.

Children may be exposed to CDDs from ingestion of contaminated soil or by contact of contaminated soil with their skin. However, skin contact with contaminated soil will result in much less CDDs entering the blood stream than if they ingest contaminated soil. Also, the amount of CDDs that will pass to the blood stream after eating contaminated soil will depend on the type of soil and on how tight the CDDs are bound to the soil. Children should be restricted from playing near any known hazardous waste sites. Some children eat a lot of dirt. Discourage your children from eating dirt or from putting their toys or other foreign objects in their mouths that may be contaminated with soil. Make sure that your children wash their hands frequently, especially before eating. Discourage your children from putting their hands in their mouths or other hand-to-mouth activities.

Older children may be exposed to CDDs if they smoke cigarettes. Younger children and infants may be exposed by inhaling the second-hand smoke from their parents or other adult smokers. Parents should talk to their children about the dangers of smoking cigarettes.

You and your children are likely to be exposed to very low amounts of CDDs in the diet particularly when you consume meat, milk, other dairy products, and fish. This represents the major source of background exposure to CDDs in most people. Children and adults should eat a balanced diet preferably containing low to moderate amounts of animal fats including meat and dairy products, and fish that contain higher amounts of CDDs and eat larger amounts of fruits, vegetables and grains.

You or your children may be exposed to CDDs by eating certain types of fish or wildlife caught in certain locations. A number of states have advisories for CDDs in fish and shellfish species; and one state has a wildlife advisory in effect for wood ducks. Each state, Native American tribe, or U.S. Territory sets its own criteria for issuing fish and wildlife advisories. A fish advisory will specify which waterbodies have restrictions, and a wildlife advisory will specify which hunting areas have restrictions. The advisory will tell you what types and sizes of fish or game are of concern. The advisory may completely ban eating fish or game or recommend that you limit the number of meals you eat of a certain species. For example, an advisory may tell you to eat a certain type of fish no more than once a month. The advisory may also tell you only to eat certain parts of the fish or game animal and how to prepare or cook the fish or game to decrease your exposure to CDDs. Fish and wildlife advisories are often stricter for pregnant women, nursing mothers, and young children. To reduce your children's exposure to CDDs, obey all fish and wildlife advisories. Information on Fish and Wildlife Advisories in your state is available from your state Public Health Department, or state Natural Resources Department and signs may be posted in certain fishing and hunting areas.

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

Specific tests exist to measure CDD levels in samples of body fat, blood, and breast milk, but these tests are not routinely available. All people now have some levels of CDDs in their body fat and blood. Levels of 2,3,7,8-TCDD on a lipid basis are generally below 10 pg/g of lipid (ppt) in the blood and fatty tissue of the general population of the United States, and usually range from 3 to 7 ppt. Levels higher than these indicate past exposure to above-normal levels of 2,3,7,8-TCDD. Although CDDs stay in the body fat for a long time (see Section 1.4), tests are not used to determine when exposure occurred, but can be used to estimate dose of the exposure if the time of exposure is known.

Although exposure to 2,3,7,8-TCDD has been associated with adverse health effects in people, no one effect is specifically related to exposure to CDDs. There are laboratory tests which can indicate whether you have been exposed to CDDs, but these are costly and take weeks to perform and they cannot be used to predict whether you will develop harmful health effects.

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

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

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

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

The government has developed regulations and guidelines for 2,3,7,8-TCDD. These are designed to protect the public from the potential adverse health effects of the chemical. The Food and Drug Administration (FDA) recommends against consuming fish and shellfish with 2,3,7,8-TCDD levels greater than 50 ppt. Such levels have resulted in the closing of several commercial fishing areas. In addition, EPA has issued guidance to states on how to evaluate health risks to recreational and subsistence fishers, and how to issue fish consumption advisories when concentrations of CDDs in fish and shellfish pose a risk to these populations. Currently, 66 health advisories have been issued by 21 states restricting consumption of fish and wildlife contaminated with CDDs. EPA also has recommended limits on how much 2,3,7,8-TCDD can be present in drinking water. EPA advises that children should not have more than 1 nanogram 2,3,7,8-TCDD per liter of water (ng/L) (ppt) in 1 day, or more than 0.01 ng/L per day for long-term exposure.

For long-term exposure in adults, EPA recommends that there should not be more than 0.04 ng/L (ppt) in drinking water.

Human milk can contain higher levels of CDDs than cow's milk. Therefore, breast-fed infants can be exposed to higher levels of CDDs on a body weight basis than adults. The World Health Organization (WHO) has concluded that this risk to infants does not outweigh the positive biological and psychological benefits of breast-feeding at general population levels of dioxins. However, the specific concentration at which CDD levels in human milk would lead to harmful health effects in infants has not yet been determined.

Regulation of many of the sources of CDDs appears to have been successful in reducing the amount of CDDs entering the ecosystem and in decreasing the potential for human exposure. EPA and ATSDR listed 2,3,7,8-TCDD as hazardous substance. Many regulations govern its destruction and disposal. See Chapter 7 for more information on regulations and guidelines.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

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

* Information line and technical assistance

Phone: 1-800-44701544
Fax: (404) 639-6359

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

* To order toxicological profiles, contact:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

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 of the toxicology of chlorinated dibenzo-*p*-dioxins (CDDs).

CDDs are a class of related chlorinated hydrocarbons that are structurally similar. The basic structure is a dibenzo-*p*-dioxin (DD) molecule comprised of two benzene rings joined via two oxygen bridges at adjacent carbons on each of the benzene rings. There are eight homologues of CDDs, monochlorinated through octachlorinated. Each homologous class contains one or more isomers or congeners. The family of CDDs contains 75 congeners—2 monochlorodibenzo-*p*-dioxins (MCDD), 10 dichlorodibenzo-*p*-dioxins (DCDD), 14 trichlorodibenzo-*p*-dioxins (TrCDD), 22 tetrachlorodibenzo-*p*-dioxins (TCDD), 14 pentachlorodibenzo-*p*-dioxins (PeCDD), 10 hexachlorodibenzo-*p*-dioxins (HxCDD), 2 heptachlorodibenzo-*p*-dioxins (HpCDD), and a single octachlorodibenzo-*p*-dioxin (OCDD). The seven 2,3,7,8-chlorine substituted congeners are the most toxic CDD congeners, with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) being one of the most toxic and most extensively studied. This compound is often called "TCDD" or merely "dioxin" in the popular literature. **Chlorinated dibenzofurans (CDFs) are structurally and toxicologically related chemicals as are certain “dioxin-like” PCBs; the reader is encouraged to consult the toxicological profile for CDFs (ATSDR 1994) and the toxicological profile for PCBs (ATSDR 1996) for information on the health effects associated with exposure to these groups of chemicals.**

2.1 HUMAN STUDIES

This section presents information on human health effects, including those known to be associated and those possibly associated with exposure to CDDs (primarily 2,3,7,8-TCDD). Since limited data exist to assign a specific route of exposure (inhalation, oral, dermal) to human studies, the information in this section is organized by health effects—death, systemic, immunological, neurological, developmental, reproductive, 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).

The human studies discussed in this section are of populations known to reside or work in environments with above-background levels of CDDs and related compounds. Data on health effects in humans following exposure to CDDs have come from studies on accidental, occupational, and residential exposure and from studies on the use of 2,3,7,8-TCDD-contaminated pesticides. Because a number of these studies examined several end points, brief descriptions of these CDD-exposed populations are included in this section. Several factors complicate the interpretation of data regarding health effects in humans following exposure to CDDs; these include incomplete exposure data, concomitant exposure to other compounds, and a small number of participants, which limits the statistical power of the study to detect adverse health effects. Many of the studies on health outcomes following exposure to 2,3,7,8-TCDD and related compounds did not monitor exposure levels or internal dose. Surrogates of exposure were often used to identify potentially exposed populations and the level of exposure; some of the more commonly used surrogates include chloracne (a dermal condition generally indicative of appreciable exposure), potential exposure to phenoxy herbicides known to be contaminated with 2,3,7,8-TCDD, living in the vicinity of an accidental release of substances containing CDDs and related compounds, or an area with CDD-contaminated soil. Some of the more recent studies have used blood lipid CDD levels as a measure of internal dose in order to quantify exposure in individuals. In many of these studies, serum 2,3,7,8-TCDD levels were measured a number of years after exposure termination. CDDs are highly persistent lipophilic compounds which are resistant to biodegradation and have a great potential to bioaccumulate. Thus, a single chemical analysis of blood or adipose tissue represents a measure of past cumulative exposure to CDDs. With the assumptions of first-order kinetics for the elimination of 2,3,7,8-TCDD and an elimination half-life of 7–12 years, it is possible to extrapolate or adjust the serum or adipose tissue lipid concentration of 2,3,7,8-TCDD back to the time of the original excess exposure which may have occurred many years earlier, if the time of original exposure is known. Body burden or total dioxin amount can then be calculated from the serum 2,3,7,8-TCDD levels using the assumption that the concentration of 2,3,7,8-TCDD in serum lipid is in equilibrium with total body lipid 2,3,7,8-TCDD concentrations and that in an average adult 22% of the body weight is lipid. Body burdens were calculated (see Table 2-1) for the human studies reporting serum (or tissue) lipid 2,3,7,8-TCDD concentrations. If only current serum 2,3,7,8-TCDD levels were reported, then half-life-adjusted serum levels and body burdens were calculated using a half-life of 8.5 years (Michalek et al. 1996) and 22% body fat for a 70 kg adult (DeVito et al. 1995). A number of studies have calculated half-life-adjusted serum 2,3,7,8-TCDD levels; in these cases, the reported half-life adjusted serum 2,3,7,8-TCDD levels were used to estimate body burdens. Egeland et al. (1994), Jansing and Korff (1994), and Wolfe et al. (1995) calculated half-life adjusted serum 2,3,7,8-TCDD levels using a half-life of approximately 7 years. The 7.1-year half-life was derived from a study of 36 veterans involved in Operation Ranch Hand (Pirkle

Table 2-1. Health Effects in Humans Associated with Estimated 2,3,7,8-TCDD Body Burdens

Exposure duration	Effect	Current serum levels[a] (pg/g lipid)		Estimated levels at the time of exposure termination[b]		Elimination half-life (years)	Reference
		Mean	Range	Serum level (pg/g lipid)	Body burden[c] (ng/kg)		
<1	Chloracne in children	19144	828-56,000	NA	2876[d]	NA	Mocarelli et al. 1991
<1	No increased risk of spontaneous abortion	NR	>10	>110[e]	>24	7.1	Wolfe et al. 1995
≥15	No increased risk of clinical gastrointestinal disease	220	NR	1,900[f]	493	NR	Calvert et al. 1992
≥15	No increased risk of clinical hepatic disease	220	NR	1,900[f]	493	NR	Calvert et al. 1992
NR	Chloracne in 5/7 subjects	185	36-291	5,920[g] 1,047[h]	1480 262	5 10	Schecter et al. 1993
11	Chloracne	604	163-1,935	2,935[i]	646	7	Jansing and Korff 1994
6.5	Immunosuppression	330	43-874	942-1,108[j]	207-244	8.5	Tonn et al. 1996
≥15	No increased risk for peripheral neuropathy	252	2-3,390	2,240[f]	493	NR	Sweeney et al. 1993
<1	Change in sex ratio of children	540-mother 791-father	126-1,650 104-2,340	NA	119[k] 174	NA	Mocarelli et al. 1996
≥15	Increased prevalence of high luteinizing hormone and low testosterone levels	NR	20-3,400	140-30,000[l]	31-6,600	7.1	Egeland et al. 1994
≥1	Increased cancer mortality rate	418	NR	1408-8444[m]	310-1,858	8.5	Fingerhut et al. 1991

Table 2-1. Health Effects Associated with Exposure to 2,3,7,8-TCDD and Body Burdens in Humans (continued)

Exposure duration	Effect	Current serum levels[a] (pg/g lipid)		Estimated levels at the time of exposure termination[b]		Elimination half-life (years)	Reference
		Mean	Range	Serum level (pg/g lipid)	Body burden[c] (ng/kg)		
NR	Increased cancer mortality rate	NR	NR	NR	≥1,000[n]	5.1 or 8.9	Ott and Zober 1996
≥20 years	Increased cancer mortality rate	296	NR	321-4,296[o]	71-945	8.5	Manz et al. 1991

[a] Lipid-adjusted serum levels at the time of examination
[b] Calculated using elimination half-life and the assumption of first order kinetics for the elimination of 2,3,7,8-TCDD from the body.
[c] Unless noted, body burdens were calculated assuming the average worker weighed 70 kg with 22% body fat (DeVito et al. 1995)
[d] Calculated using serum 2,3,7,8-TCDD levels measured shortly after exposure. Body burdens were calculated using body weights of 13 kg for 1-3 year olds, 20 kg for 4-6 year olds, 28 kg for 7-10 year olds, 45 kg for 11 year old males, and 55 kg for 16 year old females (NAS 1989) and body fat percentages of 15% for 0-10 year olds, 15% for 11 year old males, and 20% for 16 year old females (ICRP 1981).
[e] Calculated by the study authors using a half-life of 7.1 years.
[f] Calculated by the study authors using an unspecified half-life.
[g] Calculated by the study authors using a half-life of 5 years; body burdens estimated by using the study authors assumption of reference body weights of 75 kg for males and 65 kg for females and 25% body fat.
[h] Same as footnote g but using a half-life of 10 years.
[i] Calculated by the study authors using a half-life of 7 years.
[j] Calculated using the mean current serum level, a half life of 8.5 years (Michalek et al. 1996), background 2,3,7,8-TCDD concentration of 5 ng/kg lipid, and 13-15 years elapsed time.
[k] Serum 2,3,7,8-TCDD levels were measured shortly after exposure.
[l] Calculated by the study authors using a half-life of 7.1 years and background dioxin levels of 6.08 pg/g lipid.
[m] Calculated using the mean current serum level, a half life of 8.5 years (Michalek et al. 1996), background 2,3,7,8-TCDD concentration of 5 ng/kg lipid, and 15-37 years elapsed time.
[n] Calculated by the study authors using half-lives of 5.1 or 8.9 for people with 20 or 30% body fat, respectively, and the individual's body weight at the time of exposure.
[o] Calculated using the reported mean current adipose tissue 2,3,7,8-TCDD level of 296 ng/kg, half-life of 8.5 years (Michalek et al. 1996), background 2,3,7,8-TCDD concentration of 5 ng/kg lipid, and 1-33 years of elapsed time.

NR Not reported; NA Not applicable, see appropriate footnote for further details.

et al. 1989). In a later study of Ranch Hand personnel, Michalek et al. (1996) calculated a mean serum 2,3,7,8-TCDD half-life of 8.5 years using blood samples collected in 1982, 1987, and 1992 from more than 300 veterans. In the studies of populations exposed several decades prior to measuring 2,3,7,8-TCDD levels in the blood, a difference of 1.4 years in the half-life can yield a large difference in estimated body burdens. For example, in the Manz et al. (1991) study, in which the workers were exposed for 33 years prior to 2,3,7,8-TCDD analysis, a body burden of 945 ng/kg at the time of exposure was calculated using a half-life of 8.5 years; using the 7.1-year half-life, the body burden would be 1606 ng/kg. See Section 2.3.4 for a more complete discussion on estimating human body burdens and the overview to Section 2.5 for information on background exposure.

Occupational exposure to CDDs most likely occurs mainly through inhalation of CDD-contaminated particles or dust and through dermal contact with solutions containing CDDs. However, data indicate that oral exposure to low levels of CDDs from contaminated food (including milk) represents the major route of environmental exposure for the general population and for people living in areas with known dioxin contamination (Connett and Webster 1987; Schecter et al. 1994a; Travis and Hattemer-Frey 1987).

Occupational Exposure. Exposures to 2,3,7,8-TCDD, one of the most potent of the CDD congeners, have occurred occupationally in workers involved in the manufacture and application of trichlorophenols and the chlorophenoxy acid herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Holmstedt (1980) has reviewed the history of industrial exposures that have occurred between 1949 and 1976, and Kogevinas et al. (1997) summarized recent data on these cohorts. The first reported cases of industrial poisoning were in 1949 at a 2,4,5-T producing factory in Nitro, West Virginia. 2,3,7,8-TCDD formation resulted from uncontrolled conditions in the reactor producing 2,4,5-trichlorophenol (2,4,5-TCP) from tetrachlorobenzene in methanol and sodium hydroxide. Approximately 228 workers (including production workers, laboratory personnel, and medical personnel) were affected. Between 1949 and 1968, 3 other explosive releases were reported: 1 involved 254 workers at the BASF AG facility in Ludwigshafen, Germany, in 1953 (Goldman 1972; Thiess et al. 1982; Zober et al. 1990, 1993); a second similar accident in 1963 involving 106 workers at Philips-Duphar facility in Amsterdam, Netherlands was a problem since the seriousness of the 2,3,7,8-TCDD exposure was not anticipated and cleanup workers were exposed (Holmstedt 1980); and the third was an explosion in a 2,4,5-TCP manufacturing facility in Coalite, England, involving 90 workers (May 1973). Holmstedt (1980) cited papers describing occupational exposure in 24 additional factories producing TCPs or 2,4,5-T during the same period of time. Exposure data on most of these incidents were limited; various numbers of workers were affected, and many of the

published reports are anecdotal. Ott et al. (1994) measured serum 2,3,7,8-TCDD levels in 138 of the 254 exposed workers several decades after the explosion at the BASF facility. More than 35 years after the explosion, serum 2,3,7,8-TCDD levels of <1–553 pg/g lipid were found; these correspond to serum levels of 3.3–12,000 pg/g lipid (calculated using a 7-year half-life) at the time of the accident.

Some of the most comprehensive studies on occupational exposure were conducted by the National Institute for Occupational Safety and Health (NIOSH). They are cross-sectional studies of workers at U.S. chemical facilities involved in the manufacture of 2,3,7,8-TCDD-contaminated products between 1942 and 1984 (Calvert et al. 1991, 1992; Egeland et al. 1994; Fingerhut et al. 1991; Sweeney et al. 1993). Serum 2,3,7,8-TCDD levels were measured in the workers at two of the plants. The mean 2,3,7,8-TCDD serum lipid level in 281 production workers in the Newark, New Jersey, and Verona, Missouri, plants was 220 ppt (range, 2–3,390 ppt) 18–33 years after exposure termination; the referent group of 260 people who had no self-reported occupational exposure and were matched by neighborhood, age, race, and sex had a mean serum 2,3,7,8-TCDD level of 7 ppt (Calvert et al. 1992; Sweeney et al. 1993). Sweeney et al. (1990) estimated current mean lipid-adjusted 2,3,7,8-TCDD levels of 293.4 ppt (range, 2–3,390 ppt) in 103 production workers at the New Jersey facility and 177.3 ppt (range, 3–1,290 ppt) in 32 workers at the Missouri facility; the mean half-life extrapolated levels (using a half-life of 7 years) were 2,664.7 ppt (range, 2–30,900 ppt) and 872.3 ppt (range, 3–6,100 ppt) in the two facilities, respectively. It should be noted that serum 2,3,7,8-TCDD levels were only measured in workers at these two facilities, and it is not known if the levels in these workers are reflective of serum 2,3,7,8-TCDD levels in workers at the other ten facilities.

There are also a number of studies of chlorophenol and phenoxy herbicide applicators. Some of these studies used job histories, questionnaires, and interviews to determine which phenoxy herbicides the workers had used. Many of the studies did not measure exposure levels or internal doses; rather, 2,3,7,8-TCDD exposure was assumed if the worker was exposed to a phenoxy herbicide known to be contaminated with 2,3,7,8-TCDD, such as 2,4,5-T. However, the level of exposure to these 2,3,7,8-TCDD-contaminated products was generally not determined.

Residential/Environmental Exposures. Several incidents in which populations were exposed to potentially high levels of 2,3,7,8-TCDD include: an industrial accident that occurred during the production of 2,4,5-TCP at the ICMESA plant in Seveso, Italy and the spraying of roads and other places with a mixture of waste oil, including chemical waste generated during the manufacture of 2,4,5-TCP, in Missouri.

The most widely studied release of 2,3,7,8-TCDD primarily involving residential exposures occurred in Seveso, Italy in 1976. The ICMESA factory produced trichlorophenol by hydrolysis of 1,2,4,5-tetrachloro-benzene with alkali in ethylene glycol. The reactor overheated and the safety valve ruptured releasing a cloud containing primarily sodium trichlorophenate but also 2,3,7,8-TCDD. It was estimated that more than 1.3 kg of 2,3,7,8-TCDD was released into the atmosphere and that more than 17,000 people in a 2.8-km^2 area adjacent to the facility were exposed. To investigate this accident, the contaminated area was separated into regions A, B, and R based on soil levels of 2,3,7,8-TCDD. The population sizes were 736, 4,737, and 31,800 in areas A, B, and R, respectively. The respective mean (and maximum) surface soil levels of 2,3,7,8-TCDD were 230 (447) $\mu g/m^2$, 3 (43.8) $\mu g/m^2$, and 0.9 (9.7) $\mu g/m^2$ for areas A, B, and R, respectively. Dividing the populations into different zones based on soil levels has been criticized because it does not take into consideration actual-exposure levels and differences in within-zone 2,3,7,8-TCDD exposure (Mastroiacovo et al. 1988). Blood and tissue samples from exposed individuals have been saved and 2,3,7,8-TCDD levels in some of the original samples and in follow-up blood samples have been analyzed. Serum 2,3,7,8-TCDD levels ranged from 828 to 56,000 ppt (lipid adjusted) in 19 residents of zone A (Mocarelli et al. 1991).

Various populations in Missouri were exposed to 2,3,7,8-TCDD in 1971 and 1972 as a result of spraying approximately 29 kg of 2,3,7,8-TCDD-contaminated waste oil on horse arenas, parking lots, and residential roads for dust control (Andrews et al. 1989). The oils originated from an industrial waste residue contaminated with 2,3,7,8-TCDD at levels of 305 ppm (Needham et al. 1991). An exposed group of 51 adults have been the subject of several studies. Adipose tissue levels, as well as paired human serum levels, were measured for 36 of these persons. Sixteen of the individuals were residents of areas where roadways had been sprayed and had mean 2,3,7,8-TCDD adipose tissue levels of 21.1 ppt (range, 1.28–59.1 ppt) in 1985 (Andrews et al. 1989). Eight persons exposed to 2,3,7,8-TCDD at the horse arenas had a mean adipose 2,3,7,8-TCDD concentration of 90.8 ppt (5.0–577 ppt). In a comparison population of 57 people with no known 2,3,7,8-TCDD exposure, 2,3,7,8-TCDD levels in the adipose tissue ranged from 1.4 to 20.2 ppt, with a mean of 7.4 ppt. Although the population of study was not large, they were evaluated in depth for medical effects (Hoffman et al. 1986; Stehr et al. 1986; Webb et al. 1984).

Exposures in Vietnam. During the Vietnam war, a program of aerial spraying of herbicides, code name Ranch Hand, was conducted in 10–20% of the Republic of Vietnam. During the 9 years of the program (1962–70), 19 million gallons of herbicides were dispersed. Six herbicides were used, with Agent Orange being the primary herbicide used (11 million gallons dispersed) (Wolfe et al. 1985). Agent Orange

was a 1:1 mixture of 2,4-D and 2,4,5-T in diesel oil and contained <1–20 ppm 2,3,7,8-TCDD as a contaminant. A number of studies have examined the possible association between Agent Orange exposure and adverse health effects in Vietnam veterans and Vietnamese residents living in the area of spraying. The results of a study comparing blood 2,3,7,8-TCDD levels in Vietnam veterans and the general U.S. population found that on average there was no significant difference between blood 2,3,7,8-TCDD levels between Vietnam veterans and comparison populations (CDC 1987). Thus, "service in Vietnam" or self-reported exposure to Agent Orange is not a reliable index of 2,4,5-T or 2,3,7,8-TCDD exposure. Studies of Air Force personnel participating in Operation Ranch Hand have found increased serum 2,3,7,8-TCDD levels in some of the persons (CDC 1987; USAF 1991). The median level in serum lipids for 888 Ranch Hand personnel was 12.4 ppt (range, 0 to 617.7 ppt) in contrast to 4.2 ppt (0-54.8 ppt) in a comparison group of 856 matched Air Force personnel (Wolfe et al. 1995). The median and high serum 2,3,7,8-TCDD levels would extrapolate to original serum levels of 43 and 3135 ppt, respectively, based on 20 years of elapsed time, and a half-life of 8.5 years. Since the tour of duty in Vietnam for the majority of U.S. veterans was generally less than 1 year, the military exposure was considered to be of intermediate duration if not stated otherwise in the original study.

No studies were located, however, regarding health effects in humans exposed to CDDs by specific routes of exposure (e.g., inhalation, oral, dermal). In this profile, human health effects caused by combined exposure through various exposure routes are discussed separately from effects found in animals that were maintained under controlled experimental conditions (i.e., route, duration, and levels).

2.1.1 Death

None of the studies examining humans acutely exposed to high concentrations of 2,3,7,8-TCDD or other CDD congeners (as contrasted with long-term studies) reported acute instances of death. A number of epidemiology studies have investigated mortality in populations occupationally or environmentally exposed to 2,3,7,8-TCDD or chemicals contaminated with 2,3,7,8-TCDD or other CDD congeners. No significant increases in the number of deaths were observed in workers at phenoxy herbicide or chlorophenol manufacturing facilities (Cook et al. 1986, 1987b; Fingerhut et al. 1991; Ott et al. 1980, 1987; Zack and Suskind 1980) or in workers exposed to 2,3,7,8-TCDD as a result of the accident at the BASF AG facility in Germany (Ott and Zober 1996; Thiess et al. 1982; Zober et al. 1990). Additionally no increases in mortality were observed in the 10-year period after the Seveso accident (Bertazzi et al. 1989b) or in Vietnam veterans involved in Operation Ranch Hand (Wolfe et al. 1985). Although none of these studies found significant

increases in the overall mortality rate, several studies found statistically significant increases in cause-specific mortality. For example, Flesch-Janys et al. (1995) found a significant risk of cardiovascular disease and ischemic heart disease mortality in workers exposed to 2,3,7,8-TCDD and other congeners during the BASF AG accident, and Fingerhut et al. (1991) found a significantly increased risk of cancer mortality in phenoxy herbicide and chlorophenol production workers. More complete descriptions of significant findings in the mortality studies are presented in the appropriate effect portions of Section 2.1.

2.1.2 Systemic Effects

The effects of 2,3,7,8-TCDD exposure in humans exposed in occupational or environmental settings have been described in several studies. Few studies provided precise exposure levels. However, for some cohorts, blood lipid 2,3,7,8-TCDD levels in samples collected shortly after exposure and stored frozen for several years have been analyzed. In other studies, the original blood levels of 2,3,7,8-TCDD were estimated using 2,3,7,8-TCDD levels measured in recent blood samples, the amount of time between exposure and blood sample collection, and a mean serum half-life of 5–12 years. 2,3,7,8-TCDD body burdens calculated from available serum lipid 2,3,7,8-TCDD levels are presented in Table 2-1.

Respiratory Effects. Information regarding respiratory effects of CDDs in humans is limited. Effects of acute massive exposure in workers exposed to 2,3,7,8-TCDD in an industrial accident in Germany included bronchitis and laryngitis a few days after exposure, and hemorrhagic pleuritis 11 months after exposure (Goldman 1973). In an occupationally exposed group, decreased pulmonary function was found in smokers 10 years after the cessation of manufacture of herbicides contaminated with 2,3,7,8-TCDD as compared with nonexposed smokers (Suskind and Hertzberg 1984). In contrast with the results of Suskind and Hertzberg (1984), Calvert et al. (1991) found no significant differences in ventilatory function between a group of 281 workers employed 15 years earlier in the production of NaTCP, 2,4,5-T ester, or hexachlorophene and 260 referents. At the time of the examination, the lipid-adjusted mean serum 2,3,7,8-TCDD concentration was 220 ppt in the exposed workers compared to 7 ppt for the referents. In addition, there was no association between previous occupational exposure to 2,3,7,8-TCDD contamination and elevation in the incidence of chronic bronchitis or in the prevalence of chronic obstructive respiratory disease. Calvert et al. (1991) suggested that the disparity between their results and those of Suskind and Hertzberg (1984) may have been due to the fact that exposed workers in the Suskind and Hertzberg (1984) study were, on average, 10 years older than controls and to the potential exposure to 2,4,5-T acid dust in that study. The 2,4,5-T

acid was finished as a liquid as opposed to a powder in the plant studied by Suskind and Hertzberg (1984), thus limiting inhalation exposure.

No respiratory effects were associated with exposure to 2,3,7,8-TCDD-contaminated herbicides in a group of Vietnam Air Force veterans involved in Operation Ranch Hand examined more than 10 years after the war (Wolfe et al. 1985). In the 1987 follow-up (USAF 1991), no association was found between the initial or current serum level of 2,3,7,8-TCDD and incidences of asthma, bronchitis, pleurisy, pneumonia, or tuberculosis; abnormal spirometric measurements were often associated with CDD blood levels, but according to the authors (USAF 1991), the differences in the mean level between high- and low-exposure subjects were not clinically important. The authors suggested that these findings may have been related to the association between 2,3,7,8-TCDD and body fat because obesity is known to cause a reduction in vital capacity.

A recent follow-up of the cohort involved in the Seveso accident reported a significant increase in deaths (4 deaths) from chronic obstructive pulmonary disease in males from zone A (relative risk [RR]=3.7; 95% confidence internal [CI]=1.4–9.9) and in females from zone B (7 deaths; RR=2.4; 95% CI=1.1–5.1) (Pesatori et al. 1998). The excess found among zone A males was mainly detected in the first 5 years after the accident and mainly affected elderly men. As mentioned below under Cardiovascular Effects among this cohort, Pesatori et al. (1998) stated that stress related to the disaster experience could have precipitated early deaths among people with pre-existing chronic respiratory disease. The investigators also speculated that 2,3,7,8-TCDD, through immunotoxic action, may have impaired protection and defense against episodes of respiratory infection, which play a major role in the natural history of chronic obstructive respiratory disease.

The existing information suggests that acute exposure to high levels of CDDs may cause respiratory effects mainly as a response to upper respiratory tract irritation, but evidence from the numerous cohorts exposed to 2,3,7,8-TCDD that have been studied suggests that the respiratory system is not a target for 2,3,7,8-TCDD toxicity.

Cardiovascular Effects. Most earlier data indicated that exposure to CDDs does not induce cardiovascular effects (Bond et al. 1983; Moses et al. 1984; Suskind and Hertzberg 1984). In a cross-sectional health survey in 1979 of 226 workers who had potential exposure to 2,3,7,8-TCDD from 1948 to 1969 in 2,4,5-T production, 52% had chloracne (present for a mean of 26 years) which was used as a surrogate for heavy exposure. When the chloracne group was compared to workers without chloracne (low

exposure rather than unexposed workers), there was an increased reported incidence of angina and myocardial infarction; when these data were age-adjusted, the prevalence was not statistically increased (Moses et al. 1984). Examination of West Virginia TCP production workers revealed no increases in the prevalence of hypertension or coronary artery disease, abnormal ECG findings, atherosclerotic changes on chest X-ray, or blood pressure elevation (Suskind and Hertzberg 1984).

Cardiovascular examination did not reveal any changes in 17 individuals who were treated for dermal lesions following acute exposure to 2,3,7,8-TCDD in the Seveso industrial accident (Reggiani 1980) or in a group of Missouri residents living in 2,3,7,8-TCDD-contaminated areas for a chronic period of time (mean 2.8 years in one area, 4.9 years in others) (Hoffman et al. 1986). In the 10-year period following the Seveso accident, there was a significant increase in the relative risk (RR) of death from chronic ischemic heart disease in men (RR=1.56; 95% CI=1.2–2.1), which was predominantly due to the increased risk during the first 5-year period (RR=1.76; 95% CI=1.2–2.5) (Bertazzi et al. 1989a). When the residents were divided into contamination zones, the relative risks of death from chronic heart disease in zones A, B, and R were 5.16 (95% CI=1.3–20.9), 1.57 (95% CI=0.6–4.2), and 1.72 (95% CI=1.2–2.5), respectively, for the first 5-year period and 3.28 (95% CI=0.8–13.2), 0.96 (95% CI=0.4–2.6), and 1.61 (95% CI=1.2–2.2), respectively, for the 10-year period (Bertazzi et al. 1989b). In females, there was an increased risk of death from chronic rheumatic heart disease (RR=1.54; 95% CI=0.7–3.2) during the 10-year period (Bertazzi et al. 1989a), which was predominately due to the high relative risk in women living in zone A (RR=27.58; 95% CI=8.5–89.9) (Bertazzi et al. 1989b). Bertazzi et al. (1989b) noted that increased risk of cardiovascular disease deaths may have been due to post-accident stress rather than to 2,3,7,8-TCDD exposure. The results of a 5-year follow-up were recently published (Pesatori et al. 1998). The recent analysis reported five deaths in males from chronic ischemic heart disease (RR=3.0; 95% CI=1.2–7.3); three deaths in females from chronic rheumatic heart disease (RR=15.8; 95% CI=4.9–50.4); and three deaths, also in females, from hypertensive vascular disease (RR=3.6; 95% CI=1.2–11.4), all from zone A, the most severely affected area. Although these observations suggest an association between exposure to 2,3,7,8-TCDD and incidence of cardiovascular effects, they do not necessarily show that the effects were caused by 2,3,7,8-TCDD. As previously suggested by Bertazzi et al. (1989a), Pesatori et al. (1998) also indicates that the disaster experience with its burden of psychosocial stressors may have played a major role in the increased deaths found.

No cardiovascular effects were observed in a group of Air Force veterans exposed to 2,3,7,8-TCDD-contaminated herbicides during the Vietnam war and examined several years post-exposure (Wolfe et al.

1985). However, a follow-up study of the Ranch Hand cohort reported increased mean diastolic blood pressure in those with current serum lipid 2,3,7,8-TCDD levels from 15 to 33.3 ppt, but not in subjects with higher 2,3,7,8-TCDD serum levels (USAF 1991). In addition, the proportion of abnormally low peripheral pulses in all Ranch Hand veterans, regardless of serum levels, was elevated relative to a comparison group. Also, arrhythmias detected on the electrocardiogram were significantly associated with 2,3,7,8-TCDD exposure, but there was no consistent dose-response relationship.

Flesch-Janys et al. (1995) found significant increases in mortality from heart and circulatory diseases in workers exposed to 2,3,7,8-TCDD and other CDD congeners during the accident at BASF AG. Relative risks for cardiovascular disease and ischemic heart disease mortality were 1.96 (95% CI=1.15–3.34) and 2.48 (95% CI=1.32-4.66), respectively, for workers with extrapolated serum lipid 2,3,7,8-TCDD levels of $348 pg/g (ppt) (current 2,3,7,8-TCDD levels were used to estimate 2,3,7,8-TCDD levels at the end of exposure). Additionally, statistically significant dose-response trends for increasing cardiovascular and ischemic heart disease deaths were found. The risk for cardiovascular and ischemic heart disease deaths also increased as the serum lipid CDD and CDF levels increased. However, the results from the Flesch-Janys et al. (1995) study are difficult to interpret since the percentage of chemical workers who died from cardio-vascular disease was 38% compared to 49% for a referent group from a gas supply company with no known special exposure to CDDs/CDFs. An international study comprising 36 cohorts from 12 countries and a total of 21,863 workers exposed to phenoxyacid herbicides and chlorophenols followed from 1939 to 1992 detected an increased risk for death from cardiovascular disease, especially ischemic heart disease (RR=1.67; 95% CI=1.23–2.26) among the exposed workers (Vena et al. 1998). Risks did not differ across latency categories or by year of first exposure, but increased slightly by duration of exposure except for those with 20 or more years of exposure. Vena et al. (1998) indicate, however, that the study was hampered by the reliance on mortality and the crudeness and inaccuracies of death certificate diagnoses. Furthermore, they noted that possible confounding effects from important risk factors for ischemic heart disease such as cigarette smoking, high fat diet, blood pressure, obesity, physical inactivity, and serum lipids cannot be ruled out.

In contrast with the positive findings described in the studies summarized above, a recent study of 281 workers employed 15 years earlier in the manufacturing of 2,4,5-trichlorophenol at two U.S. chemical plants and 260 unexposed referents found no significant association between 2,3,7,8-TCDD exposure and adverse cardiovascular effects (Calvert et al. 1998). The mean serum 2,3,7,8-TCDD concentrations (on a lipid basis) were 220 ppt in the workers and 7 ppt in the referents. Among the workers, the mean 2,3,7,8-TCDD

concentration when occupational exposure ceased was estimated to have been 1,900 ppt using a 7-year estimated half-life for serum 2,3,7,8-TCDD. Cardiovascular outcomes examined included myocardial infarction, angina, cardiac arrhythmias, hypertension, and abnormal, peripheral arterial flow. Calvert et al. (1998) indicated that although the study had sufficient statistical power to detect an elevated risk for cardiac arrhythmias, hypertension, and abnormal peripheral arterial flow, it had low power (approximately 50%) to detect an elevated risk for myocardial infarction and angina and concluded that further examination of the association between exposure to 2,3,7,8-TCDD and cardiovascular diseases is necessary.

In summary, there is suggestive but inconclusive evidence of adverse cardiovascular effects in humans exposed to relatively high concentrations of CDDs. Increased deaths from chronic heart disease were observed among the Seveso cohort, but psychosocial factors could not be ruled out; no clear dose-response relationships were seen among the Ranch Hand cohort; increased deaths from heart and circulatory disease were reported among German workers exposed to CDDs; and no evidence of adverse cardiovascular effects was detected among U.S. workers exposed to CDDs.

Gastrointestinal Effects. Earlier studies of individuals with exposure to substances contaminated with 2,3,7,8-TCDD found significant elevations in self-reported ulcers (Bond et al. 1983; Suskind and Hertzberg 1984), but a study of Vietnam veterans (USAF 1991) failed to find such effects. A more recent study evaluated the gastrointestinal effects of exposure to substances contaminated with 2,3,7,8-TCDD in an occupational cohort (Calvert et al. 1992). More than 15 years earlier, the workers were employed in the manufacture of trichlorophenol and its derivatives at 2 chemical plants. A total of 281 workers participated in the medical study; the control group consisted of 260 unexposed subjects who lived in the same communities as the workers. The participants underwent a comprehensive physical examination of the abdomen and rectum. The mean serum 2,3,7,8-TCDD level (on a lipid basis) for the workers was 220 ppt and was found to be highly correlated with years of exposure to 2,3,7,8-TCDD-contaminated substances; controls had a mean serum 2,3,7,8-TCDD concentration of 7 ppt. At the time of examination, the workers were not found to be at increased risk for any gastrointestinal diseases. Moreover, neither gastrointestinal ulcer disease nor gastritis was found to be significantly associated with any measure of 2,3,7,8-TCDD exposure, as determined by logistic regression analysis. The only significant finding from the physical examination was a statistically significant association between decreased anal sphincter tone and 2,3,7,8-TCDD exposure. This, however, was attributed to examiner bias since all those that exhibited reduced sphincter tone were examined by the same physician (two physicians conducted the blind

examinations). The results of these studies suggest that there is no association between occupational exposure to 2,3,7,8-TCDD and gastrointestinal disease.

Hematological Effects. Human studies regarding exposure to 2,3,7,8-TCDD or 2,3,7,8-TCDD-contaminated chemicals did not find any overt hematological effects after intermediate- (Wolfe et al. 1985) and chronic-duration exposures (Stehr et al. 1986).

Contact with 2,3,7,8-TCDD-contaminated soil in Missouri by physical or recreational activities for 6 months at 100 ppb or for 2 years at 20–100 ppb resulted in a slight but statistically significant increase in total white blood cell (WBC) counts using a prevalence test (5.3% were increased above 10,000 WBC/mm^3 compared to 0.7% for controls, but the increase was slight) (Hoffman et al. 1986). A follow-up study of the same population found no differences in the number of red blood cells, white blood cells, or platelets between exposed and nonexposed individuals (Evans et al. 1988). In a similar cohort, Stehr et al. (1986) found no consistent differences in hematology parameters in a high-risk group (68 persons) compared to a low-risk group (36 persons) except a slightly elevated platelet count. No significant differences in total leukocyte, granulocyte, or lymphocyte levels were observed between workers with high serum lipid CDD and CDF levels and workers with lower serum CDD and CDF levels (Neubert et al. 1993).

A health study of Vietnam veterans involved in Operation Ranch Hand indicated an association between high initial and current serum 2,3,7,8-TCDD levels and increased erythrocyte sedimentation (Wolfe et al. 1995), and an earlier study by Wolfe et al. (1985) indicated an increase in mean corpuscular volume; however, these changes were minor and were not observed in the 1991 follow-up (USAF 1991). Higher serum 2,3,7,8-TCDD levels were also associated with positive dose-response trends for increases in white blood cell and platelet levels.

The existing information suggests that CDDs, at the body burdens seen in the studied populations, do not cause adverse hematological effects.

Musculoskeletal Effects. The only information available comes from two anecdotal reports. In one of them, two individuals exposed to 2,3,7,8-TCDD in a horse arena that was sprayed with waste oil for dust control complained of painful joints (arthralgia) (Kimbrough et al. 1977). In the second case, a chemist exposed to 2,3,7,8-TCDD and 2,3,7,8-tetrabromo-p-dibenzo dioxin (2,3,7,8-TBDD) complained of muscle

pain in the lower extremities and back (Schecter and Ryan 1991). The role that 2,3,7,8-TCDD played in these cases, if any, is unknown. No further information was located.

Hepatic Effects. Two of three laboratory workers synthesizing or working with 2,3,7,8-TCDD in the laboratory developed chloracne 8 weeks after potential acute exposures (Oliver 1975). Blood cholesterol levels (the only biochemical change) were elevated in all three workers and remained elevated for two years. Biochemical examinations were conducted on 55 male workers in Prague who were admitted into a hospital in 1968 and 1969 suffering from chronic 2,3,7,8-TCDD intoxication from exposure in a plant producing 2,4,5-T (Pazderova-Vejlupkova et al. 1981). The first symptoms of intoxication included chloracne (present in the majority of the workers) and neurological symptoms; levels of exposure were never measured. Hypercholesterolemia was seen in 56% of the patients, hyperlipemia in 67%, hyperphospholipidemia in 42%, diabetes mellitus in 8%, a low glucose tolerance level in 19%, increased α and γ globulins in 42% and uroporphyria in 21% (the study did not include a referent group) (Jirasek et al. 1976; Pazderova-Vejlupkova et al. 1981). Liver biopsies revealed mild steatosis, periportal fibrosis, and activated Kupffer cells in those examined. At 10 years postexposure, most of the biochemical changes were not detected; only cholesterol levels remained high (Pazderova-Vejlupkova et al. 1981). Transient alterations of liver function tests were reported in workers exposed to 2,3,7,8-TCDD following an industrial accident in Great Britain (May 1973). Jennings et al. (1988) found nonsignificant increases in serum cholesterol and triglycerides but no effect on gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), or creatinine in a group of 18 workers in England who had been exposed 17 years previously, when comparisons were made with a group of 15 carefully matched controls.

Mocarelli et al. (1986) conducted a 6-year study on clinical laboratory parameters of children exposed to 2,3,7,8-TCDD following the Seveso accident. ALT, aspartate aminotransferase (AST), GGT, alkaline phosphatase, cholesterol, and triglycerides in plasma and delta amino levulinic acid in urine were monitored yearly in exposed and control groups beginning in June, 1977, approximately 1 year after the incident. The children were 6–10 years old at the time of the accident; 69, 528, and 874 resided in the A, B, and R zones, respectively. Chloracne was seen in 19, 0.7, and 4.6%, of the children in areas A, B, and R, respectively. Blood samples were drawn from 69, 83, and 221 children in areas A, B, and R, respectively. A slight increase in GGT and ALT occurred in the highest exposure group (based on zone of residences) compared to controls, but the values were not considered abnormal and returned to baseline levels within 3 years of the initial exposure. 2,3,7,8-TCDD blood levels have been more recently analyzed in about 30 of the subjects (Mocarelli et al. 1991). Similarly altered biochemical values (mainly increased serum transaminases and

GGT) were reported much earlier in individuals residing in an area of Seveso with average soil 2,3,7,8-TCDD concentrations of 580.4 μg/m^2 (Pocchiari et al. 1979). A study of clinical chemistry parameters and urinary porphyrins in Missouri residents living in a 2,3,7,8-TCDD-contaminated area did not indicate any definitive changes that were of clinical importance in 154 persons (high-risk, based on soil levels of dioxins) exposed for up to 11 years (Webb et al. 1989). Multivariate regression analysis with number of years of residence as a surrogate of dose gave a positive trend for GGT and alkaline phosphatase.

A medical survey of workers employed more than 15 years earlier in the manufacture of sodium trichlorophenol and its derivatives at two chemical plants found no evidence of an elevated risk for clinical hepatic disease at the time of examination (Calvert et al. 1992). The cohort consisted of 282 workers and 260 unexposed matched controls. Exposure was assessed by measuring lipid-adjusted serum 2,3,7,8-TCDD levels. The mean serum 2,3,7,8-TCDD level in the workers was 220 ppt, compared with 7 ppt in the control group. The results from abdominal and rectal examination were unremarkable. Similarly, the results from blood and urine tests measuring liver function showed no statistically significant differences between exposed workers and controls, with the exception of a statistically significantly higher mean GGT level in workers. Also, workers were found to have a statistically significant elevated risk for an out-of-range GGT level compared with referents. However, multivariate analysis with logistic regression showed a statistically significant interaction between 2,3,7,8-TCDD exposure and lifetime alcohol consumption, indicating that the elevated risk for an out-of-range GGT was confined to those workers with a history of alcohol consumption and that the risk among the alcohol-consuming workers for an out-of-range GGT increased with increasing 2,3,7,8-TCDD level.

In a follow-up study, Calvert et al. (1996) examined the association between exposure to 2,3,7,8-TCDD and serum lipids. In the follow-up the authors chose not to adjust the 2,3,7,8-TCDD serum concentrations for total lipids to avoid the problems of interpretation that would arise when adjusting a covariate by the dependent variable. Consequently, the results obtained in this study cannot be compared directly with those from the Operation Ranch Hand study (see below). The median serum 2,3,7,8-TCDD concentration among the workers was 406.6 femtograms/g serum (fg/g) compared with 36.9 fg/g among the referents. The results of logistic regression analyses revealed an association between serum 2,3,7,8-TCDD and risk for an abnormally decreased HDL cholesterol concentration that approached statistical significance ($p=0.09$) after controlling for body weight index, use of beta-blocker medication, age, diabetes, and employment at the two plants. The concentration of 2,3,7,8-TCDD was not associated with having either an abnormal total cholesterol concentration or an abnormal total cholesterol/HDL cholesterol ratio. When the workers were

stratified into quartiles according to their serum 2,3,7,8-TCDD concentration, and after controlling for important confounders, those with the highest 2,3,7,8-TCDD concentrations (1,516–19,717 fg/g) had an elevated risk for an abnormal HDL cholesterol concentration (odds ratio [OR]=2.2; 95% CI=1.1–4.7). A small but statistically significant association between triglyceride concentration and serum 2,3,7,8-TCDD was also found (p=0.05) after controlling for gender, plant location, body weight index, cumulative cigarette consumption, use of beta-blocker medication, race, and diabetes. However, in the logistic analyses, abnormal triglyceride concentration was not associated with serum 2,3,7,8-TCDD concentration (p=0.21). Analysis by quartiles showed that workers with the highest 2,3,7,8-TCDD serum concentration had a statistically significant elevation in mean triglyceride concentration compared with the referent group. However, no significant trend was observed in the quartile analyses that evaluated risk for an abnormal triglyceride level. Calvert et al. (1996) concluded that the associations of serum 2,3,7,8-TCDD concentration with triglycerides and HDL (high density lipoprotein) cholesterol were small when compared with the influence of many other factors.

A health study in Vietnam veterans involved in Operation Ranch Hand found no liver diseases linked to 2,3,7,8-TCDD exposure, but biochemical examinations revealed a pattern suggestive of a subclinical effect on lipid metabolism (USAF 1991). Blood triglycerides showed a strong positive association with both the initial levels of 2,3,7,8-TCDD and the current serum levels; the authors indicated that this variable is highly sensitive to body fat, which was increased in the more highly exposed individuals. Cholesterol, HDL, and the cholesterol-HDL ratio also showed significant associations with 2,3,7,8-TCDD.

In conclusion, hepatotoxic effects, such as elevated GGT levels and small alterations in lipid profile, have sometimes been observed in humans following exposure to high 2,3,7,8-TCDD levels. In general, the effects are mild and in some cases appear to have been transient.

Information regarding hepatic effects observed in infants exposed perinatally to CDDs and structurally related compounds is presented in Section 2.5 under Developmental Effects.

Renal Effects. A child who played in a sand box contaminated with waste oils containing 2,3,7,8-TCDD developed hemorrhagic cystitis and focal pyelonephritis (Kimbrough et al. 1977). Since chloracne was not seen and levels of 2,3,7,8-TCDD in the sand were not provided, the effects cannot be definitely attributed to 2,3,7,8-TCDD exposure. No renal effects were reported in other individuals exposed at the same location. An early study in Missouri residents chronically exposed to a 2,3,7,8-TCDD-contaminated environment

found increased incidence of self-reported urinary problems, leukocyturia, and microscopical hematuria (Webb et al. 1984). However, the results of urinalysis on this group did not indicate any kidney effects (Hoffman et al. 1986; Stehr et al. 1986). No renal effects were found in a group of Vietnam veterans exposed to 2,3,7,8-TCDD in Agent Orange based on case histories and evaluation of five laboratory variables comparing Ranch Hand veterans and the various comparison groups (USAF 1991; Wolfe et al. 1985, 1990). Kidney lesions have not been reported in any of the several studies on occupational exposure or for exposed cohorts in Seveso, Italy. These studies suggest that the kidney is not a target organ of 2,3,7,8-TCDD toxicity in humans.

Endocrine Effects. Jennings et al. (1988) examined thyroid function in a group of 18 workers exposed to 2,3,7,8-TCDD as a result of an industrial accident during the manufacture of 2,4,5-T. At the time of the study, 17 years after the accident, all the workers appeared healthy. No measure of exposure was provided. An unexposed group of 15 subjects served as controls. The end points monitored were serum thyroxine (T4), triiodothyronine (T3), and thyroid stimulating hormone (TSH). Without providing further details, the authors indicated that none of the subjects studied had biochemical evidence of thyroid dysfunction. A 35-year follow-up study of workers exposed to 2,3,7,8-TCDD during the BASF accident found a significant increase in the incidence of thyroid disease, as compared to an age-matched referent group (Zober et al. 1994). The workers were divided into two groups based on back-calculated (using a 7-year half-life) serum lipid 2,3,7,8-TCDD levels of $1,000 ppt and <1,000 ppt. For both groups of 2,3,7,8-TCDD-exposed workers, the incidence of thyroid disease was significantly higher than for the referent group, but did not differ between the two groups of workers.

Endocrine function was assessed in Vietnam veterans involved in Operation Ranch Hand. A strong positive association was found between glucose intolerance or increased risk of diabetes and 2,3,7,8-TCDD serum levels (USAF 1991). The diabetes finding remained significant even after adjusting for body fat. Furthermore, subclinical effects in thyroid function (significant decrease in mean T3 uptake and increases in mean TSH) were reported for Operation Ranch Hand veterans with high current 2,3,7,8-TCDD serum levels of $33.3 ppt (USAF 1991). However, the magnitude of the differences was not considered physiologically significant. A follow-up study of Operation Ranch Hand veterans provides further information on the association between serum 2,3,7,8-TCDD levels and the incidence of diabetes mellitus and glucose and insulin levels (Henriksen et al. 1997). The cohort consisted of 989 exposed subjects and 1,276 comparison individuals who served in Southeast Asia (54) during the same period but who were not involved with spraying herbicides. Initial dioxin levels were computed using a first-order pharmacokinetic model with a

constant half-life of 8.7 years. Four exposure categories were defined: 1) comparisons, with current dioxin levels of #10 ppt; 2) background Operation Ranch Hand veterans, with current dioxin levels of #10 ppt; 3) low category, with initial dioxin levels exceeding 10 ppt but #94.2 ppt; and 4) high category, with initial dioxin levels >92.4 ppt. Adjustments were made for age, race, and military occupation. The current median dioxin levels in the low and high categories were 15.0 and 46.2 ppt, respectively. The results of the analysis showed an increase in glucose abnormalities (RR=1.4; 95% CI 1.1, 1.8), diabetes prevalence (RR=1.5; CI 1.2, 2.0), and use of oral medications to control diabetes (RR=2.3; CI 1.3, 3.9) and a decrease in the time-to-diabetes onset with dioxin exposure. Serum insulin abnormalities increased in nondiabetics. Henriksen et al. (1997) pointed out that although some unknown confounder may not have been adjusted for, the strengths of the study included high participation and low attrition rates and accurate serum dioxin measurement and that, taken together, the results indicated a possible relation between dioxin exposure and diabetes mellitus, glucose metabolism, and insulin production. A follow-up evaluation of a cohort from the Seveso accident population found a significant increase in deaths from diabetes among women from zone B (RR=1.9; 95% CI=1.1–3.2) (Pesatori et al. 1998). Thirteen deaths were reported and 9 out of the 13 occurred in the second decade after the accident (RR=3.1; 95% CI=1.6–6.1). Pesatori et al. (1998) indicated that the fact that only women were affected might be explained by the systematically higher 2,3,7,8-TCDD concentrations in females than in males.

In summary, the evidence available from epidemiological studies suggests that exposure to high concentrations of CDDs may induce long-term alterations in glucose metabolism and subtle alterations in thyroid function.

Information regarding endocrine effects observed in infants exposed perinatally to CDDs and structurally related compounds is presented in Section 2.5 under Developmental Effects.

Dermal Effects. The most commonly observed effect of 2,3,7,8-TCDD exposure in humans is chloracne (Jirasek et al. 1976; Kimbrough et al. 1977; May 1973; Oliver 1975; Reggiani 1980). Chloracne is characterized by follicular hyperkeratosis (comedones) occurring with or without cysts and pustules (Crow 1978). Unlike adolescent acne, chloracne may involve almost every follicle in an involved area and may be more disfiguring than adolescent acne (Worobec and DiBeneditto 1984). Chloracne usually occurs on the face and neck, but may extend to the upper arms, back, chest, abdomen, outer thighs, and genitalia. In mild cases, the lesions may clear several months after exposure ceases, but in severe cases they may still be present 30 years after initial onset (Crow 1978; Moses and Prioleau 1985). In some cases lesions may

resolve temporarily and reappear later. Scarring may result from the healing process. Other chlorinated organic chemicals can also cause chloracne.

Acute exposure to 2,3,7,8-TCDD in a chemical laboratory induced the development of chloracne in two of three individuals within 8 weeks of the exposure (Oliver 1975). Chloracne occurred in workers occupationally exposed to 2,3,7,8-TCDD during the manufacture of herbicides (Bond et al. 1989b; Moses and Prioleau 1985; Poland et al. 1971) and after industrial accidents in several locations throughout the world (Goldman 1973; May 1973; Moses et al. 1984; Pocchiari et al. 1979; Suskind and Hertzberg 1984).

Accidental exposure to 2,3,7,8-TCDD in a 1949 explosion in a trichlorophenol plant in Nitro, West Virginia, resulted in an outbreak of severe chloracne. Moses et al. (1984) conducted a cross-sectional survey of workers in this plant in 1979. In reviewing the impact of the accident, the authors indicated that 117 workers had severe chloracne as a result of the explosion; however, 111 additional workers were found to have had chloracne prior to the explosion. A cross-sectional study of 226 workers in 1979 indicated that 52% had chloracne which persisted for 26 years, and in 29 subjects it was still present after 30 years. Blood levels were not measured, but the air dust in the plant was suspected to have contained 2,4,5-T contaminated with 6 ppm 2,3,7,8-TCDD compared to 0.1 ppm in later years. Similarly, high incidences of chloracne were also found in other facilities (Jirasek et al. 1976; May 1973; Poland et al. 1971; Vos et al. 1978). Appearance of chloracne after accidental occupational exposure may be immediate or delayed; since workers may not always be removed from the work environment, the duration of exposure and total exposure is difficult to assess.

Skin lesions from environmental exposures to 2,3,7,8-TCDD have been most thoroughly studied in the population exposed in Seveso, Italy. Reggiani (1980) described dermal lesions for 17 persons (primarily children) hospitalized shortly after the accidental release in Seveso. Acute lesions probably due to alkali and burns were observed immediately and had a duration of up to 2 months; chloracne in children occurred within 2 weeks (earliest occurrence was 3 days) and usually persisted for 8–26 months. Irritative lesions (characterized by erythema and edema of exposed areas, vesiculobollus and necrotic lesions, and papulonodular lesions) were observed in 447 people in Seveso 20–40 days after the accident, and 34 of these individuals later developed chloracne (Caputo et al. 1988). In 1976 and 1978, there were 193 childhood cases of chloracne and 17 of the most severe were in zone A where soil levels were the highest. Bisanti et al. (1980) reported that in zone A, 46 early cases (3–6 months) and 15 late cases (7–10 months) of chloracne were seen, and in zone B, 9 delayed cases were observed. In all zones, 50 early- and 143 late-appearing

cases of chloracne were reported (Caputo et al. 1988). In the 193 people with chloracne, the comedones and cysts progressively decreased in the 2 years following the accident (Caputo et al. 1988). In the most severe cases, regression of the lesions began at the end of 1978. All affected children were clear of lesions by 1982. Histological examination of the lesions from the limbs of severe chloracne patients revealed orthokeratotic hyperkeratosis with loss of adhesiveness, particularly near the follicular ostia; dilated follicular ostia filled with cornified lamellae; acanthosis; horny metaplasia with possible acrosyringeal cyst formation in the dermal and intradermal eccrine duct; and foreign body granulomas around the detached wall of the excretory ducts of some eccrine sweat glands (Caputo et al. 1988). Thirty of the 30,000 samples of serum collected and frozen in 1976 (10 zone A residents with the most severe cases of chloracne types 3 and 4 [chloracne was rated as type 1 for the mildest form to type 4 for the most severe cases], 10 former zone A residents who did not develop chloracne, and 10 controls from non-contaminated zones) were analyzed by Mocarelli et al. (1991). 2,3,7,8-TCDD blood levels (lipid adjusted) of 12,100–56,000 ppt were observed in 6 children with type 4 chloracne and levels of 828, 1,690, 7,420 ppt were found in 3 children with type 3 chloracne. In adults, levels of 1,770–10,400 ppt were associated with no chloracne. No chloracne was observed in Missouri residents who had adipose 2,3,7,8-TCDD levels of 5.2–59.1 ppt 16 years after exposure (using a half-life of 8.5 years, peak tissue levels of 6–204 ppt can be estimated) or in Operation Ranch Hand veterans. While there is a higher incidence of this disorder in those with higher serum 2,3,7,8-TCDD levels, interindividual variability makes it difficult to specify a dose that will result in chloracne (Needham et al. 1991).

The results of a further examination of Operation Ranch Hand veterans was recently published (Burton et al. 1998). The cohort consisted of 930 exposed subjects and 1,200 comparison individuals who served in SEA during the same period but who were not involved with spraying herbicides. The authors examined the associations between serum dioxin levels and a) chloracne, b) occurrence of acne relative to the tour of duty in SEA, and c) anatomical location of acne after service in SEA. Initial dioxin levels were computed using a first-order pharmacokinetic model with a constant half-life of 8.7 years. Four exposure categories were defined: 1) comparisons, with current dioxin levels of #10 ppt; 2) background Operation Ranch Hand veterans, with current dioxin levels of #10 ppt; 3) low category, with current dioxin levels exceeding 10 ppt but #94.2 ppt; and 4) high category, with dioxin levels >92.4 ppt. Adjustments were made for age, race, and military occupation. The range of initial dioxin levels in the low and high categories was 27.7–94.1 ppt and 94.2–3,290 ppt, respectively. Because physicians did not find any cases of chloracne among Operation Ranch Hand veterans at any physical examination and no cases were found via medical record review, the analysis was restricted to cases of acne. The results showed that among Operation Ranch Hand veterans

who had acne only after their service in SEA, the prevalence of acne at any location was increased in the high-exposure category, but the adjusted odds ratio relating acne in the eye-ear-temple location and dioxin category was increased for all three Operation Ranch Hand exposure categories. The increase was greatest in the background exposure category (OR=1.3; 95% CI=0.8–2.2). According to Burton et al. (1998), the results suggest that the Operation Ranch Hand exposure to dioxin, which was much lower than the Seveso exposure, was insufficient for the production of chloracne or that the exposure may have caused chloracne that resolved and was currently undetectable.

The incidence of chloracne was examined in a group of 3 men and 4 women who were among 231 workers exposed to dioxins at a chemical factory in Ufa, Russia, approximately 25 years prior to blood collection in 1991 and 1992 (Schecter et al. 1993). Five of the seven (three males and two females) were diagnosed with chloracne after working in the manufacture of 2,4,5-T contaminated with 2,3,7,8-TCDD between 1965 and 1967. Blood analysis showed 2,3,7,8-TCDD levels (on a lipid basis) ranging from 36 to 291 ppt (mean 185 ppt) in 1991 and 1992 compared with a mean of 4.4 ppt from a sample of 68 subjects from the general Russian population. Polychlorinated dibenzofurans and "dioxin-like" polychlorinated biphenyls (PCBs) were also detected, but it was estimated that in the workers, 2,3,7,8-TCDD contributed over 60% of the total dioxin equivalents (2,3,7,8-TCDD plus "dioxin-like" CDDs and PCBs). One of the workers diagnosed with chloracne had the lowest 2,3,7,8-TCDD blood concentration of the group, whereas two workers with higher levels did not display chloracne. This suggested that the presence of chloracne indicates exposure to dioxin (or similar chlorinated chemical), but its absence does not preclude such exposure, as noted by others (Mocarelli et al. 1991). Schecter et al. (1993) estimated that in the workers, the dioxin toxic equivalents (TEQ) in 1967 ranged from 226 to 1,707 ppt, assuming a 10-year half-life, and from 1,173 to 9,366 ppt assuming a 5-year half-life (see Section 2.5 for a detailed explanation on TEQs and toxicity equivalent factors [TEFs]). They also estimated the total 2,3,7,8-TCDD body burden for the workers to have been between 22 and 172 µg using a 5-year half-life and 4–30 µg using a 10-year half-life (mean present body burden was 3.2 µg versus 0.072 µg for general population). According to Schecter et al. (1993), this is the first reported incidence of chloracne in females with elevated dioxin blood levels from occupational exposure.

A group of 8 individuals who had contracted chloracne between 1973 and 1976 while working in the manufacture of TCP or in the maintenance of a TCP plant were examined 15 years after the exposure (Jansing and Korff 1994). Slight residual chloracne was diagnosed in two subjects, but otherwise the workers were healthy. 2,3,7,8-TCDD levels in blood ranged from 163 to 1,935 ppt (lipid basis), and by assuming a half-life of 7 years, the authors estimated that the blood concentration during the exposure had

ranged from 545 to 9,894 ppt. It was found that the concentration of 2,3,7,8-TCDD in blood correlated well (r=0.93) with duration of chloracne if 2 subjects with a disposition to hypersensitive skin reactions were not included in the analysis.

Other effects manifested as dermal changes have also been noted to accompany chloracne. In addition to chloracne, hyperpigmentation and hirsutism (also known as hypertrichosis or abnormal distribution of hair) were also reported in 2,3,7,8-TCDD-exposed workers (Jirasek et al. 1976; Oliver 1975; Poland and Smith 1971; Suskind and Hetzberg 1984). In the cohort examined by Suskind and Hetzberg (1984), hypertrichosis was observed 25 years after exposure, particularly among workers with persistent chloracne upon clinical examination. In contrast, Moses et al. (1984) found no evidence of hypertrichosis, even though 31% of the exposed workers had evidence of residual chloracne. Webb et al. (1989) observed three cases of hypertrichosis, but not hyperpigmentation, among Missouri residents, one with serum levels of <20 pg/g and two with levels between 20 and 60 pg/g. However, neither condition was noted on examination among residents of the Quail Run Mobile Home Park (Hoffman et al. 1986). Actinic or solar elastosis was also observed among a group of workers diagnosed with active chloracne at the time of their examinations in 1979 (Suskind and Hertzberg 1984).

In conclusion, dermal effects, particularly chloracne, are the most commonly reported effects of 2,3,7,8-TCDD exposure in humans because they are easy to identify. Additional information is needed to determine the level and frequency of 2,3,7,8-TCDD exposure needed to cause chloracne and whether individual susceptibility plays a role in the etiology. Also, chloracne in humans indicates CDD exposure, but lack of chloracne does not indicate that exposure has not occurred. Other dermal conditions reported include hypertrichosis, hyperpigmentation, and solar elastosis.

Ocular Effects. Eye irritation, which correlated with severity of chloracne, was reported by Poland et al. (1971) among workers employed in a 2,4,5-T factory; however, the role of 2,3,7,8-TCDD, if any, cannot be determined.

Body Weight Effects. Limited information was located regarding body weight effects in humans following exposure to CDDs. A transient weight loss was reported in a laboratory worker following an acute exposure to 2,3,7,8-TCDD (Oliver 1975). Weight loss associated with severe cases of chloracne was mentioned in a study among herbicide-manufacturing workers (Jirasek et al. 1976), but further information regarding weight loss was not provided.

2.1.3 Immunological Effects

A limited number of studies have examined the immunotoxicity of 2,3,7,8-TCDD in humans. Most of these studies have found potential alterations in lymphocyte populations (e.g., T cells, B cells), cell surface markers (e.g., $CD4RO^+$, $CD8^+$), or lymphoproliferative responses. The interpretation of these studies is limited by the lack of data correlating changes in immune function measurements and changes in host resistance to disease challenges (Kerkvliet 1995). Based on medical insurance records, Zober et al. (1994) found a significant increase in the incidence of infectious and parasitic disease in 2,3,7,8-TCDD-exposed workers in the 35-year period after the BASF accident. When the workers were divided into groups based on the severity of chloracne or back-calculated serum lipid 2,3,7,8-TCDD levels (assuming a half-life of 7 years), the increase in infectious disease was significant only in the group with severe chloracne and the group with 2,3,7,8-TCDD levels of $1,000 ppt. Among the workers with severe chloracne, one disease subcategory, intestinal infections, accounted for the increased incidence of infectious diseases. A two-fold increase in the incidence of upper respiratory tract infections was also observed in the cohort. Dividing the workers into various groups did not result in evidence of increased respiratory infections in a particular group. Zober et al. (1994) also found a significantly higher incidence of appendicitis in 2,3,7,8-TCDD workers; it is not known if this effect was the result of immunotoxicity or a direct effect on the appendix. Although the results of this study suggest a relationship between 2,3,7,8-TCDD exposure and an increased risk of infection, the authors note that the difference may reflect differences in medical care use between the workers and the referent group. Jennings et al. (1988) examined immunological parameters in a group of 18 workers 17 years after an industrial accident during the manufacture of 2,4,5-T in Coalite, England. At the time of the study all members of the cohort were apparently healthy. An unexposed group of 15 subjects served as controls. No measure of exposure was provided. The exposed group had a significantly increased number of natural killer (NK) cells, and concentration of antinuclear antibodies and immune complexes. Total lymphocytes, B cells, T cells, T-helper cells, T-suppressor cells, the lymphoproliferative response to phytohemagglutinin, and serum levels of immunoglobulins were similar between exposed and control groups. An immunological assessment of 41 subjects exposed to 2,3,7,8-TCDD-contaminated soil in Times Beach, Missouri was conducted by Webb et al. (1989). Sixteen participants had 2,3,7,8-TCDD adipose tissue levels <20 ppt, 13 had levels between 20 and 60 ppt, and 12 had levels >60 ppt. The highest level was 750 ppt. Results from multiple regression analysis showed that increased 2,3,7,8-TCDD levels correlated with an increased percentage and total number of T lymphocytes. The increase was due to $CD8^+$ and $T11^+$ T cells; $CD4^+$ T cells were not altered in percentage or number. The lymphoproliferative responses to T cell mitogens or tetanus toxoid were not altered, and neither was the cytotoxic T cell response. Serum

immunoglobulin A (IgA) was increased, but IgG was not. The study subjects did not exhibit any clinical disease associated with the 2,3,7,8-TCDD levels. In contrast with Webb's findings, depressed cell-mediated immunity was found in residents from the Quail Run Mobile Home Park in Missouri (Hoffman et al. 1986); however, repeated examination of the group failed to confirm the observation (Evans et al. 1988). The levels of 2,3,7,8-TCDD in adipose tissue from this group were unknown.

No indications of immune disease were found in a group of 8 subjects who had worked in a TCP manufacturing plant 15 years earlier and had elevated blood levels of 2,3,7,8-TCDD (163–1,935 ppt) at the time of the examination (Jansing and Korff 1994). The only significant observation was that individuals with the greater exposure (judged by 2,3,7,8-TCDD blood levels and duration of chloracne) showed a tendency of lower gamma-globulin levels. Neubert et al. (1993) examined surface receptors on lymphocyte subpopulations of workers with moderately increased body burden of 2,3,7,8-TCDD and of other CDDs and CDFs. The group consisted of 89 volunteers involved in decontamination work at a chemical plant in Hamburg, Germany. The volunteers were grouped according to their body burden, as defined by the CDD concentration in blood (on a lipid basis). Four groups were formed: a low-, medium-, and higher-level reference group, and the exposed group. Their respective median 2,3,7,8-TCDD blood concentrations were 2, 5, 11, and 41.5 ppt. 2,3,7,8-TCDD was a minor contributor to the total dioxin equivalents. Regression analysis of the data showed some slight trends for some of the biomarkers, such as $CD45R0^{+}$. Except for one, all the trends were increases. The slight increase in the percentage of $CD4^{+}CD45R0^{+}$ cells remained significant even after accounting for age-related changes. The authors concluded that altogether, the data did not provide any evidence for a decrease in cellular components of the human immune system in subjects with moderately increased CDD/CDF body burden. They also pointed out that adult humans appear to be less susceptible to this action of CDDs than adolescent marmoset monkeys. In a follow-up study, Neubert et al. (1995) examined lymphocyte proliferation responses (measured as ^{3}H-thymidine incorporation) in the same volunteers. They found no decrease in the capacity of ^{3}H-thymidine incorporation with any of the proliferation stimulators in the group with the increased 2,3,7,8-TCDD body burden, compared with the other groups. A recent study examined the long-term effects of 2,3,7,8-TCDD on immune function in 11 industrial workers in Germany who had been exposed for several years to high doses of 2,3,7,8-TCDD 20 years earlier (Tonn et al. 1996). Current 2,3,7,8-TCDD blood concentrations (lipid basis) ranged from 43 to 874 ppt, compared with about 4 ppt as the average for the German population. Ten matched unexposed subjects served as controls. End points monitored included determination of lymphocyte subsets, and immunocompetence of T- and B-lymphocytes by mitogen-induced lymphoproliferation assays and by assays using sensitive mixed-lymphocyte cultures. At the time of the study, the workers were generally

healthy, although five persons still exhibited chloracne. Analysis of lymphocyte subsets showed no differences between the control and the 2,3,7,8-TCDD-exposed group. Moreover, there was no statistically significant difference in the response to mitogen stimulation between the two groups, and no correlation was found between individual 2,3,7,8-TCDD levels in the blood or the age of the person and the respective proliferative capacity of their lymphocytes. However, exposed subjects showed a reduced response to human lymphocyte antigen-allogeneic lymphocytes and interleukin-2-boosted proliferation. According to Tonn et al. (1996), this suppression is indicative of a reduced T-helper cell response, although the actual number of T-helper cells was not altered by 2,3,7,8-TCDD. The authors concluded that 2,3,7,8-TCDD immunosuppression is more likely mediated by a reduced functionality of individual cells rather than by a reduction in numbers of cells circulating in the blood. Tonn et al. (1996) further noted that the changes in immunocompetence observed did not correlate with obvious diseases related to severe immunodeficiency such as certain cancers and infections.

In a study of 192 persons exposed to 2,3,7,8-TCDD (and CDFs) in a pesticide-producing factory in Germany, there was also no correlation between the levels of 2,3,7,8-TCDD in blood from exposed workers and the frequency of infectious diseases (Jung et al. 1998). The investigators also conducted a number of assays such as immunoglobulins, serum electrophoresis, monoclonal bands, surface markers, autoantibodies, lymphocyte proliferation, the rise of tetanus antibody concentrations after vaccination, and the *in vitro* resistance of lymphocytes to chromate to evaluate the morphologic and functional state of the immune system. A subgroup of 29 most highly exposed workers was compared to a control group of 28 subjects not exposed to above background levels of 2,3,7,8-TCDD. The median concentration of 2,3,7,8-TCDD in the workers was 217 pg/g blood lipid (range, 33.6–2,252) compared to 3.9 pg/g in the controls (range, 2.9–6.0). There was no significant correlation between the current 2,3,7,8-TCDD concentrations and alterations in any of the immune parameters among the entire exposed group. In addition, the results of the tetanus vaccination and the chromate resistance test were not correlated with exposure to 2,3,7,8-TCDD. The only significant finding was that the chromate resistance of lymphocytes stimulated with phytohemagglutinin of highly exposed persons was significantly lower than that for the control group. This, according to Jung et al. (1998), suggested that the function of lymphocytes can be stressed and possibly impaired by high exposure to 2,3,7,8-TCDD. A separate report on the same group of workers found no significant exposure-related alterations in the phenotype and function of peripheral blood mononuclear cells (PBMC) as judged by the proportions of CD3, CD4, or $CD8^+$ T-lymphocytes; of $CD16^+$ natural killer cells; and of $CD19^+$ B-lymphocytes (Ernst et al. 1998). However, in the 2,3,7,8-TCDD exposed workers, the proportion of $CD8^+$ memory T-cells ($CD45RO^+$) was significantly higher, and that of lymphocytes with naive phenotype

($CD45RA^+$) was significantly lower than in PBMC of the control group. Also, *in vitro* tests of T-cell activation showed a significantly reduced interferon γ release in diluted whole blood cultures but not in isolated PBMC cultures of the TCDD-exposed cohort when T-cells were stimulated with tetanus toxoid. Based on these results, Ernst et al. (1998) suggested that exposure to high concentrations of 2,3,7,8-TCDD can partially impair in the blood milieu those T-cell/monocyte interactions that are essential for antigen-specific T-cell responses, whereas isolated PBMC in the same donor appeared functionally less affected.

The immune status of children exposed to 2,3,7,8-TCDD in the Seveso incident was also examined (Mocarelli et al. 1986). The group consisted of 44 children, 20 of whom had chloracne. The results of the testing showed no abnormalities in serum immunoglobulin concentrations, levels of circulating complement, or lymphoproliferative responses to T- and B-cell mitogens. However, a different cohort of 2,3,7,8-TCDD-exposed children examined 6 years after the explosion showed a significant increase in complement protein levels, which correlated with the incidence of chloracne (Tognoni and Bonaccorsi 1982). The children also had increased numbers of peripheral blood lymphocytes and increased lymphoproliferative responses. No specific health problems were correlated with exposure to 2,3,7,8-TCDD in these children. The findings from the Tognoni and Bonaccorsi (1982) study suggest that chloracne is a more sensitive toxicological endpoint than immunological effects because alteration in complement levels is a subclinical effect and correlated with the incidence of chloracne.

A health study of Vietnam veterans involved in operation Ranch Hand did not find any correlations between clinically significant immunological alterations and serum 2,3,7,8-TCDD levels (USAF 1991). The only significant positive association with exposure to 2,3,7,8-TCDD was an increase in serum IgA levels. The authors suggested that this alteration was indicative of a subtle inflammatory process, but there was no other evidence for an inflammatory response.

Parameters of immunocompetence were assessed in a group of 23 men with high fish consumption from the Baltic Sea (Svensson et al. 1994). Twenty men with almost no fish consumption served as controls. The parameters examined included WBC, lymphocyte levels, serum immunoglobulin levels, and lymphocyte subsets. The mean dioxin equivalent concentration (TEQ, includes CDDS, CDFs, and dioxin-like PCBs) in blood (lipid basis) from fish eaters (n=7) was 64 pg TEQ/g (range, 18–88 pg/g) compared to 21 pg TEQ/g (18–33 pg/g) for controls (n=4). CDDs and CDFs were the major contributors to the total dioxin equivalents in blood. Of all the parameters examined, only the level of NK cells was reduced in fish eaters, but the difference between groups was not statistically significant. No correlation was found between blood levels of

2,3,7,8-TCDD and the reduction in NK levels, but weak correlations existed between the latter and some non-ortho-PCB congeners and p,p′-DDT.

In conclusion, while some studies are suggestive, no consistent exposure-related immunological effects have been observed in human populations exposed to levels of CDDs several orders of magnitude higher than background exposure. This may in part be due to the lack of functional assays of immune competence in humans.

Information regarding immunological effects observed in infants exposed perinatally to CDDs and structurally related compounds is presented in Section 2.5 under Developmental Effects.

2,3,7,8-TCDD human body burdens calculated from available serum lipid 2,3,7,8-TCDD levels are presented in Table 2-1.

2.1.4 Neurological Effects

Symptoms of intoxication including lassitude, weakness of the lower limbs, muscular pains, sleepiness or sleeplessness, increased perspiration, loss of appetite, headaches, and mental and sexual disorders were reported in several of the 117 workers with severe chloracne who had been exposed to 2,3,7,8-TCDD in an occupational setting (Moses et al. 1984; Suskind 1985). Neurological symptoms persisted in these individuals for up to 10 years based on an increased incidence of sensory findings. Similar symptoms of intoxication were observed in a trichlorophenol factory in Czechoslovakia (Jirasek et al. 1976) for which a 10-year follow-up of 55 of the 80 affected workers was conducted (Pazderova-Vejlupkova et al. 1981). At autopsy, damage to peripheral neuron Schwann cells was confirmed in a worker who died (Jirasek et al. 1976). Polyneuropathy and encephalopathy were found in 23 and 7% of the surviving workers, respectively (study did not include a referent group). Most patients suffered from peripheral neuronal lesions of the lower extremities (confirmed by electromyography). Encephalopathy developed in older individuals (aged 50 and above) and was accompanied by an organic psychosyndrome due to atherosclerosis of cerebral arteries. The most-affected patient developed paroxysms of temporal epilepsies and external and internal hydrocephalus. Patients with polyneuropathy did not improve during 10 years postexposure (Pazderova-Vejlupkova et al. 1981). Similarly, neurological effects that included peripheral neuropathy, sensory impairment, tendency to orthostatic collapse, and reading difficulties were reported in workers exposed to 2,3,7,8-TCDD in an industrial accident in Germany (Goldman 1973).

Several studies have investigated the neurological effects of 2,3,7,8-TCDD in Seveso residents. Residents in zone A and zones B and R participated in a neurological screening test in 1977 (Pocchiari et al. 1979). Of the 446 residents in zone A, 6.7% and 3.1% had evidence of "idiopathic clinical neurologic damage" or "idiopathic subclinical neurologic damage" respectively, as compared to 1.2% and 1.2%, respectively, in the 255 residents in zones B or R. No definitions of clinical or subclinical damage were provided. The authors did note that the most frequently observed effects occurred in the peripheral nervous system (particularly reduced nerve conduction velocity, which was considered a subclinical effect). In 1978, 205 residents in zone A were re-tested. At this time, 11.7% had clinical damage and 4.9% had subclinical damage. No relationship between chloracne and neurological symptoms was found (Pocchiari et al. 1979). In another study of zone A residents, 22 cases of peripheral neuropathy were observed in the 470 residents examined in 1977 (prevalence rate of 8.9%, 95% confidence interval [CI] of 6.2 to 11.6) (Filippini et al. 1981). Peripheral neuropathy was diagnosed based on the occurrence of neurological symptoms (paresthesia, hypesthesia, pain, and hyposthenia), clinical signs (superficial and deep sensory impairment, muscular weakness, and tendon hypo- or areflexia), and/or electrophysiological alterations. During a re-evaluation in 1978, 26 of the 308 subjects had neurological symptoms, clinical signs, and/or altered electrophysiological readings and 16/308 had two or more electrophysiological abnormalities (at least one being altered nerve conduction velocity). The 42 subjects with evidence of peripheral neuropathy were divided into three groups: 1) residents with existing predisposing factors (e.g., excess alcohol consumption, diabetes, nutritional diseases), 2) residents with potential high exposure to 2,3,7,8-TCDD (assessed via increased serum levels of several hepatic enzymes [GGT, AST, ALT] and/or chloracne), and 3) remaining residents. The prevalence rate ratio was significantly higher in the first two groups (2.6, 95% CI=1.2–5.6 for predisposing factors group and 2.8, 95% CI=1.2–6.5 for high 2,3,7,8-TCDD exposure group) as compared to the third group. In a 6-year follow-up of 152 subjects with chloracne in Seveso, Barbieri et al. (1988) found no clear-cut peripheral neuropathy but an increase in clinical and electrophysiological signs of peripheral nervous system involvement when compared to 123 age- and sex-matched controls. In 1985, 141 of these subjects were re-examined (Assennato et al. 1989). No statistically significant alterations in motor nerve conduction velocity of the median or peroneal nerves or sensory nerve conduction velocity of the sural nerve, as compared to 167 matched controls, were observed.

No significant increases in neurological effects (based on self-reported neurological effects and neurological examination) were observed in 68 Missouri residents with potential high risk exposure to 2,3,7,8-TCDD as compared to 36 residents with low-risk exposure (Stehr et al. 1986). Abnormal neurological symptoms were observed in a group of 41 Missouri residents with measured 2,3,7,8-TCDD serum lipid levels (Webb et al.

1989). The symptoms included abnormal pain sensation in lower extremities, abnormal vibratory sensation, and abnormal reflexes. However, the distribution of these effects among residents with serum lipid 2,3,7,8-TCDD levels of <20 ppt, 2–60 ppt, or >60 ppt was not dose-related.

Nerve conduction velocities were measured in 55 employees of a 2,4,5-T and 2,4-D manufacturing facility in Jacksonville, Arkansas (Singer et al. 1982). Statistically significant decreases in median motor nerve and sural nerve conduction velocities were observed, as compared to a control group of workers not exposed to phenoxy herbicides. No effect on median sensory nerve conduction velocity was found. Sural nerve conduction velocity was significantly inversely correlated with duration of employment.

Psychological effects have been associated with 2,3,7,8-TCDD exposure in some human studies. Personality changes were reported following acute exposure (Oliver 1975). Depression (Levy 1988; Wolfe et al. 1985), hypochondria, hysteria, and schizophrenia (Wolfe et al. 1985) were found more often in Vietnam veterans exposed to 2,3,7,8-TCDD-contaminated herbicides than in the control group of veterans. A battery of tests used for the psychological evaluation included Minnesota Multiphasic Personality Inventory, Cornell, Wechsler Memory Scale I, Wechsler Adult Intelligence Scale, Wide Range Achievement Test, and Halstead-Reitan Neuropsychological Battery. Peper et al. (1993) reported that the results of neuropsychological testing of 19 persons living in an area with high concentration of dioxins in soil in Germany were within the range of values expected from standardized age samples. However, increased levels of dioxins in blood (but not substantially different from a national sample) were associated with a reduction of cognitive performance in verbal conceptualization, mnemonic organization of verbal and visual stimuli, psychomotor slowing, and a variety of subjective complaints. The concentration of CDDs (including CDFs) in blood (lipid basis) ranged from 16.1 to 80.4 ppt (TEQ), with a mean of 31 ppt. The authors recognized, however, that given the small number of subjects and the relatively low amount of exposure (monitored by blood levels) the results must be interpreted with caution.

A health study in Vietnam veterans involved in Operation Ranch Hand reported that elevated serum 2,3,7,8-TCDD levels were not associated with any neurological disease and were not related to verified psychological or sleep disorders (USAF 1991). In a more recent study, Sweeney et al. (1993) compared the prevalence of chronic peripheral neuropathy in a group of workers employed 15 years earlier in the manufacture of sodium trichlorophenol and its derivatives at two chemical plants. The cohort consisted of 265 exposed workers and an unexposed matched comparison group of 244 subjects. Exposure was assessed by measuring lipid-adjusted serum 2,3,7,8-TCDD levels. The neurologic status was evaluated through a

standardized neurological examination and electrophysiologic measurements and quantitative sensory tests of thermal and vibratory sensitivity. The results showed that the workers had a significantly higher mean serum 2,3,7,8-TCDD level (220 ppt) compared to controls (7 ppt). In both worker and referent groups, 32% met the case definition for peripheral neuropathy; however, logistic regression analyses revealed that serum 2,3,7,8-TCDD level was not related to peripheral neuropathy. The results suggested that despite continued elevated serum 2,3,7,8-TCDD levels, peripheral neuropathy is not a long-term sequela of exposure to TCDD-contaminated chemicals. Nevertheless, the authors (Sweeney et al. 1993) indicated that the study could not preclude the occurrence and subsequent resolution of acute effects caused by high exposure, as observed in Seveso (Fillippini et al. 1981; Pocchiari et al. 1979) and possibly in early case reports (Goldman 1973; Jirasek et al. 1976; Oliver 1975).

The overall evidence from case reports and epidemiological studies showed that exposure to CDDs is associated with signs and symptoms of both central and peripheral nervous system shortly after exposure. In some cases, the effects lasted several years. However, evaluation of individuals 5 to 37 years after the last exposure has not revealed any long-lasting abnormalities.

Information regarding neurological effects observed in infants exposed perinatally to CDDs and structurally related compounds is presented in Section 2.5 under Developmental Effects.

2.1.5 Reproductive Effects

A number of studies have investigated the possible association between 2,3,7,8-TCDD exposure and reproductive toxicity in humans. A common limitation of many of these studies, particularly those conducted prior to the development of assays to quantify serum and adipose levels of 2,3,7,8-TCDD, is the lack of adequate exposure data (Sweeney 1994).

The effects of 2,3,7,8-TCDD exposure on gonadal function (production of germ cells and secretion of sex hormones) has not been extensively investigated. A health study in Vietnam veterans involved in Operation Ranch Hand found a significant association between decreased testicular size and serum 2,3,7,8-TCDD levels, but no association was found for low serum testosterone levels (USAF 1991). When the Operation Ranch Hand cohort was re-examined in 1992 using ultrasound methodology, no significant alterations in testes size were found (Henriksen et al. 1996). No alterations in sperm count or the percentage of abnormal sperm were observed in Vietnam veterans involved in Operation Ranch Hand (Wolfe et al. 1985). No

consistent alterations in testosterone levels, follicle-stimulating hormone (FSH) levels, luteinizing hormone (LH) levels, testicular abnormalities, sperm abnormalities, and sperm counts were found in a follow-up study of the Operation Ranch Hand cohort; reproductive parameters were assessed in 1982, 1987, and 1992 (Henriksen et al. 1996). In workers at two 2,4,5-trichlorophenol manufacturing facilities, serum 2,3,7,8-TCDD levels were positively correlated with follicle stimulating hormone and luteinizing hormone levels and inversely correlated with total testosterone levels (Egeland et al. 1994). However, the magnitude of the change in hormone levels per unit of increase in serum 2,3,7,8-TCDD levels was small. The prevalence of high luteinizing hormone levels, high follicle stimulating hormone levels, and low testosterone levels was significantly increased in workers with half-life extrapolated serum lipid 2,3,7,8-TCDD levels of $140 pg/g, $1,860 pg/g, and $140 pg/g, respectively (based on 2,3,7,8-TCDD levels extrapolated at the time occupational exposure ceased and assuming a 7.1-year half-life). The study authors note that both low testosterone and high LH levels were not observed in the same individuals. Although the number of workers with elevated or depressed hormone levels was significantly higher than in the referent group, the adjusted mean hormone levels (adjusted for age, body mass index, alcohol consumption, smoking, and diabetes mellitus) were within 20% of referent values.

A number of studies have examined pregnancy outcomes following paternal exposure or paternal and maternal exposure to 2,3,7,8-TCDD. No significant alterations in the incidence of spontaneous abortions were found in several studies of Vietnam veterans. In a case-control study conducted by Aschengrau and Monson (1989), no association was observed between paternal military service in Vietnam and the risk of spontaneous abortion (odds ratio [OR] of 0.88, 95% confidence interval [CI] of 0.42–1.86). A limitation of this study is that service in Vietnam is not an adequate exposure surrogate for 2,3,7,8-TCDD exposure; CDC (1988) found that 2,3,7,8-TCDD body burdens in Vietnam veterans were not significantly different than background levels. In a study of Air Force personnel involved in Operation Ranch Hand, no relationship between paternal 2,3,7,8-TCDD exposure (as measured by serum 2,3,7,8-TCDD levels) and the occurrence of spontaneous abortions (relative risk [RR] of 1, 95% CI=0.7–1.3 for veterans with half-life adjusted serum lipid 2,3,7,8-TCDD levels of >110 ppt) or stillbirths (RR of 1.8, 95% CI=0.7–4.7 for veterans with half-life adjusted serum 2,3,7,8-TCDD levels of <110 ppt, current levels >10 ppt; and RR of 0.3, 95% CI=0–2.3 for veterans with half-life adjusted serum 2,3,7,8-TCDD levels of >110 ppt) were observed (Wolfe et al. 1995). No significant alterations in the relative risk of stillbirths (3 stillbirths observed in 2,3,7,8-TCDD-exposed group compared to 0 in control group) or miscarriages (RR of 1.19, 90% CI=0.58–2.45) were observed in the wives of New Zealand 2,4,5-T applicators (Smith et al. 1982). It should be noted that many of the wives were occasionally exposed while helping with spray activities and

while washing contaminated clothing. An increased incidence of spontaneous abortions was reported in women living close to a herbicide manufacturing factory in Sweden (Forsberg and Nordstrom 1985). The residents were exposed to phenoxy acids, chlorophenols, 2,3,7,8-TCDD, and dibenzofurans which were released into the soil and groundwater. The small number of cases in the exposed cohort and concomitant exposure to several other chemicals limits the conclusions which can be drawn from this study.

Several studies have reported alterations in the sex ratio of children of men and women exposed to high levels of CDDs. Mocarelli et al. (1996) observed decreases in the sex ratio of children born to parents living in area A at the time of the accident in Seveso, Italy. More females than males (48 females versus 26 males; normal ratio is 100 females to 106 males) were born between April 1977 (9 months after the accident) and December 1984. Between 1985 and 1994, there was no significant alteration in sex ratio (64 females, 60 males). In nine families in which both parents lived in area A at the time of the accident, serum lipid 2,3,7,8-TCDD levels (blood samples collected at the time of the accident) ranged from 126 to 1,650 ppt and 104 to 2,340 ppt for the mothers and fathers, respectively. Basharova (1996) reported an alteration in sex ratio (more females than males) in children of workers exposed to 2,3,7,8-TCDD-contaminated 2,4,5-T at a production facility in Ufa, Russia. No additional information on the percentage of male and female children or statistical analysis of data was provided. Similarly, more females than males (51.4% versus 48.6%; 19,675 births) were born to 9,512 male workers exposed to chlorophenate wood preservatives contaminated with CDDs (Dimich-Ward et al. 1996). James (1997) statistically analyzed the results of this study and found that the sex ratio was statistically significant, as compared to the expected Caucasian live birth sex ratio of 0.514. Stockbauer et al. (1988) did not find an alteration in the sex ratio (53.% of children were males versus 51.2% in nonexposed controls) among the children of mothers potentially exposed to CDDs in the Times Beach incident. This retrospective cohort study did not monitor where the mothers or fathers lived at the time of conception. Although three studies have found alterations in the sex ratio among the offspring of exposed individuals, a causal relationship between CDD exposure and alterations in the sex ratio cannot be inferred at this time. Further investigation of this positive association is clearly warranted.

In an inadequately reported study, Phuong et al. (1989a) reported a statistically significant increase in the incidence of hydatidiform mole in families living in southern Vietnam potentially exposed to 2,3,7,8-TCDD contaminated herbicides as compared to a group of Ho Chi Minh City residents presumably never exposed to 2,3,7,8-TCDD-contaminated herbicides. In contrast, a case-control study by Ha et al. (1996) did not find a

significant association between exposure to 2,3,7,8-TCDD-contaminated herbicides and the occurrence of complete hydatidiform mole or choriocarcinoma among women living in southern Vietnam.

The results of the human reproductive toxicity studies are inconclusive. In studies which measured 2,3,7,8-TCDD levels (Egeland et al. 1994; Henriksen et al. 1996), mixed results were found for alterations in hormone levels. The Egeland et al. (1994) study of the NIOSH cohort found significant alterations in testosterone and gonadotropins, but the alterations were small, frequently not found in the same individuals, and it is not known if they would adversely affect reproductive performance. In contrast, the Henriksen et al. (1996) study of the Operation Ranch Hand cohort did not find any alterations, but the members of this cohort were exposed to lower concentrations of 2,3,7,8-TCDD and for shorter durations than the NIOSH cohort. Studies which examined pregnancy outcomes following paternal exposure (Aschengrau and Monson 1989; Smith et al. 1982) did not find increases in the incidence of spontaneous abortions and/or stillbirths. Forsberg and Nordstrom (1985) found an increased incidence of spontaneous abortions in residents likely exposed to 2,3,7,8-TCDD. However, the Aschengrau and Monson (1989), Smith et al. (1982), and Forsberg and Nordstrom (1985) studies did not measure 2,3,7,8-TCDD levels, and it is difficult to determine the level of 2,3,7,8-TCDD exposure from the data reported. Three studies found altered sex ratios among offspring of exposed individuals (Basharova 1996; Dimich-Ward et al. 1996; Mocarelli et al. 1996), but the role of CDDs could not be determined with any certainty. Without exposure information, relationships between 2,3,7,8-TCDD exposure and the risk of adverse pregnancy outcomes cannot be established.

2,3,7,8-TCDD body burdens calculated from available serum lipid 2,3,7,8-TCDD levels are presented in Table 2-1.

2.1.6 Developmental Effects

The potential for 2,3,7,8-TCDD to induce developmental effects has been examined in several populations: residents exposed to 2,3,7,8-TCDD during aerial spraying of 2,4,5-T or from accidental releases of 2,3,7,8-TCDD or 2,3,7,8-TCDD-contaminated chemicals, workers involved in manufacturing or application of phenoxy herbicides and/or chlorophenols, and Vietnam veterans. In most of the human studies, exposure was poorly characterized.

In residents of Seveso, Italy, a significant rise in the incidence of birth defects, as compared to pre-accident levels, was observed the year after the accident (Bisanti et al. 1980). A variety of birth defects were

observed, but the incidence for any particular defect was not elevated. The authors suggest that the rise in birth defects may not be related to 2,3,7,8-TCDD exposure. Prior to 1976, birth defects in Italy were usually under reported; the authors note that the reported incidences of birth defects after the accident (23 per 1,000 births) were similar to incidences reported in other western countries. Thus, the increased incidence may be reflective of the increased reporting rather than an increased number of birth defects. In a study which assessed the risk of birth defects for the 6-year period after the Seveso accident, no increases were observed for the risk of total defects (RR of 1.2, 90% CI of 0.88–1.64 for zones A and B and RR of 0.97, 90% CI=0.83–1.13 for zones A, B, and R), major defects RR of 1.02, 90% CI=0.64–1.61 for zones A and B and RR of 0.83, 90% CI=0.67–1.04 for zones A, B and R), and minor defects RR of 1.44 90% CI=0.92–2.24 for zones A and B and RR of 1.14, 90% CI=0.92–1.42 for zones A, B and R) (Mastroiacovo et al. 1988). The small number of observed birth defects limits the statistical power of this study to detect significant increases in a specific defect.

In a study of residents of Northland, New Zealand exposed to 2,4,5-T during aerial spraying, no significant alterations in the total number of birth defects were observed in children born between 1973 and 1976, as compared to the incidence in children born between 1959 and 1960 (before the aerial 2,4,5-T spraying began) (Hanify et al. 1981). Stockbauer et al. (1988) studied the Missouri cohort and found no statistically significant excess risk of birth defects among infants from exposed mothers (n=410) compared to an unexposed referent group (n=820). However, a significant increase in the incidence of talipes (incidence ratio of 1.66, 90% CI=1.2–2.29) was observed in children born after the spraying program began. The relationship between 2,4,5-T usage and the incidence of facial clefts was investigated in residents of Arkansas exposed during the spraying of rice acreage (Nelson et al. 1979). The population was divided into areas of high, medium, and low potential exposure based on herbicide application rates. Increasing trends over time in facial clefts for both the high- and low-exposure groups were observed. The authors attributed this to better case-ascertainment rather than 2,4,5-T exposure.

In the offspring of male workers at a chlorophenol manufacturing facility, no significant increases in the incidence of infant deaths, health defects, or congenital malformations were observed (Townsend et al. 1982). The adjusted odds ratio (95% CI) for infant deaths, health defects, and congenital malformations were 0.63 (0.27–1.39), 0.85 (0.6–1.21), and 0.85 (0.53–1.35), respectively, for workers exposed to any dioxin and 0.82 (0.3–2.09), 0.93 (0.6–1.43), and 1.08 (0.63–7.83) for workers exposed to 2,3,7,8-TCDD only.

Several studies investigated the outcome of pregnancies fathered by Vietnam veterans potentially exposed to 2,3,7,8-TCDD-contaminated herbicides. Two case-control studies (Aschengrau and Monson 1990; Erickson et al. 1984) have examined the risk of Vietnam veterans having a child with birth defects. The Erickson et al. (1984) study used a cohort of 7,133 infants with birth defects registered by the Metropolitan Atlanta Congenital Defects Program and 4,246 control infants; information on military service and possible exposure to Agent Orange was obtained during interviews with the mother and father. The overall risk of having a child with birth defects was not significantly increased in the Vietnam veterans (OR of 0.97, 95% CI=0.83–1.14). However, Vietnam veterans fathered a higher proportion of the children with some birth defects (spina bifida, cleft lips, and congenital tumors including dermoid cysts, teratomas, hepatoblastomas, central nervous system tumors, and Wilm's tumors) (Erickson 1984). The case group (857 infants with congenital anomalies, 61 stillbirths, and 48 neonatal deaths) and control group (998 infants) for the Aschengrau and Monson (1990) study consisted of infants delivered between August 1977 and March 1980. No significant increase in the risk of fathering a child with birth defects was observed for the Vietnam veterans (OR of 1.3, 95% CI=0.7–2.4). Among the children with birth defects, an increased risk of having one or more major systemic malformation (OR of 1.8; 95% CI=1–3.1) was reported in infants fathered by Vietnam veterans. The largest increases were reported for malformations of the nervous system, cardiovascular system, genital organs, and urinary tract. No pattern of multiple malformations was found; the only pattern of multiple malformations observed in more than one infant was ventricular septal defect and talipes. The results of these two case-control studies (Aschengrau and Monson 1990; Erickson et al. 1984) should be interpreted cautiously because there is no documentation of 2,3,7,8-TCDD exposure. CDC (1988) found that in Vietnam veterans self-reporting exposure to Agent Orange, the levels of serum 2,3,7,8-TCDD were not significantly different than levels found in a control population.

In a study of Vietnam veterans participating in Operation Ranch Hand (Wolfe et al. 1995), an increase in nervous system defects with increasing paternal serum lipid 2,3,7,8-TCDD levels was observed (statistical analysis was not performed due to the small number of defects: 3/981 in comparison group, 0/283 in Ranch Hand veterans with current 2,3,7,8-TCDD levels of #10 ppt, 2/241 in veterans with current 2,3,7,8-TCDD levels of >10 ppt and initial levels of #110 ppt, and 3/268 in veterans with current 2,3,7,8-TCDD levels of >10 ppt and initial levels of >110 ppt). However, the authors caution that this relationship is based on a limited amount of data. No relationships between paternal 2,3,7,8-TCDD exposure (based on serum 2,3,7,8-TCDD levels) and the prevalence of other birth defects were observed. In an earlier study by Wolfe et al. (1985) of Air Force personnel involved in Operation Ranch Hand, a significant increase in the number of reported neonatal deaths (no additional details provided), as compared to a comparison group of Air Force

military employees not stationed in Vietnam, was observed. The incidence of major defects, prematurity, learning disabilities, or infant deaths was not increased in the Ranch Hand personnel. A significant increase in the incidence of minor health effects such as birth marks, rashes, and neonatal jaundice was reported by the Ranch Hand veterans. It should be noted that the pregnancy outcomes were self-reported, and this finding was not corroborated by the follow-up study (Wolfe et al. 1995) which used birth certificates, medical records, and death certificates to assess possible relationships between paternal exposure to 2,3,7,8-TCDD and developmental effects in offspring. Michalek et al. (1998) examined birth records of children born between 1959 and 1992 to Operation Ranch Hand veterans. A slight increase in the incidence of preterm births (not statistically significant) was observed in the low (current CDD level of #10 ppt) and high (extrapolated initial CDD level of >79 ppt) exposure groups but not in the medium (extrapolated initial CDD level of #79 ppt) exposure group. An increase in the relative risk of infant deaths was observed in all three groups, as compared to the referent group of veterans in SEA not exposed to Agent Orange); the relative risks in the low, medium, and high groups were 3.2 (95% CI=1.0–10.3), 1.5 (95% CI=0.3–7.5), and 4.5 (95% CI=1.5–14.0). Short gestation and low birth weight were the most common causes of infant deaths. No adverse effect on intrauterine growth was observed. Michalek et al. (1998) concluded that the increased infant mortality may not be due to paternal 2,3,7,8-TCDD exposure because the risk was increased in Operation Ranch Hand cohort members with essentially background current 2,3,7,8-TCDD levels (low exposure group) and in the highest exposure group. In Vietnamese families potentially exposed to 2,3,7,8-TCDD-contaminated herbicides during the Vietnam War, a statistically significant increase in the incidence of unspecified congenital anomalies was observed as compared with a nonexposed population (Phuong et al. 1989a). Serum lipid 2,3,7,8-TCDD levels were not measured and the extent of exposure was based on subject recall of how many times they were exposed to herbicides during the Vietnam war.

The results of the available developmental studies in humans were inconclusive. The lack of exposure data, small sample sizes, and the lack of reliable data for birth defect rates prior to 2,3,7,8-TCDD exposure limit the power of the human studies to determine if an association between 2,3,7,8-TCDD exposure and developmental toxicity exists.

2.1.7 Genotoxic Effects

Data regarding genotoxic effects in humans exposed to CDDs are inconclusive. A statistically significant increase in the incidence of cells with chromosomal aberrations and a greater number of aberrations were found in fetal tissues from induced abortions in women possibly exposed to 2,3,7,8-TCDD after the Seveso

accident (Tenchini et al. 1983). The results from cytogenetic analysis of maternal tissues were comparable to those of the control group. Furthermore, no increase in the frequency of chromosomal aberrations was found in 17 individuals who were treated for chloracne following the Seveso accident (Reggiani 1980). An increased incidence of chromosomal aberrations was found in a group of 10 Vietnam veterans (Kaye et al. 1985); however, in another study, no increases in chromosomal aberrations or sister chromatid exchanges were reported in 15 Vietnam veterans (Mulcahy et al. 1980). None of these studies included 2,3,7,8-TCDD dosimetry and all were limited by using exposed groups that were relatively small (less than 20 individuals) to have the statistical power to reliably assess the cytogenetic damage. A more recent study examined the incidence of chromosomal aberrations and of sister chromatid exchanges in human lymphocytes in 27 workers whose current 2,3,7,8-TCDD concentrations in blood were above 40 ppt, and in 28 age-comparable referents (Zober et al. 1993). The results showed no statistically significant differences between the two groups in the percentages of gaps, chromatid or chromosome exchanges, chromatid or chromosome breaks/fragments/deletions, multiple aberrations, or the overall percentage of aberrations including or excluding gaps. In the exposed group there was an increased rate of sister chromatid exchanges per cell and a higher percentage of cells with more than 10 sister chromatid exchanges. However, these associations were no longer significant when smoking status was included as covariate. Moreover, neither current nor back-calculated 2,3,7,8-TCDD concentration was a significant predictor of these parameters. Zober et al. (1993) indicated that some limitations such as the small number of individuals studied, a possible selection effect, and the possibility that some effects were transient should be considered in the interpretation of the results. The human data on the genotoxicity of 2,3,7,8-TCDD is inconsistent and inconclusive. The lack of exposure data, small sample sizes, and the inconsistent results precludes drawing conclusions from these studies.

2.1.8 Cancer

The carcinogenicity of 2,3,7,8-TCDD in humans has been assessed in numerous case-control and mortality cohort studies of chemical manufacturing and processing workers and phenoxy herbicide and chlorophenols applicators, Vietnam veterans exposed to Agent Orange, and residents of Seveso, Italy. A major weakness in many of these studies is the lack of adequate exposure data. Exposure levels or 2,3,7,8-TCDD body burdens were not measured, rather surrogates of exposure such as exposure to chemicals contaminated with 2,3,7,8-TCDD or chloracne were used to identify subjects likely exposed to 2,3,7,8-TCDD. Another major weakness of most of the human cancer data is concomitant exposure to other compounds. The focus of this discussion on the carcinogenic potential of 2,3,7,8-TCDD and other CDDs will be on studies that have documented exposure by measuring blood levels or in which exposure can be reasonably presumed. The

section is divided into four parts: 1) the effect of CDD exposure on overall cancer risk in workers involved in the manufacture or application of phenoxy herbicides or chlorophenols followed by a discussion of specific types of cancer in this group, 2) cancer risks in Vietnam veterans, 3) cancer risks in Seveso residents, and 4) conclusive statement.

Increases in the overall cancer risk were observed in a number of large cohort mortality studies of chemical manufacturing workers and phenoxy herbicide applicators (Becher et al. 1996; Fingerhut et al. 1991; Hooiveld et al. 1998; Kogevinas et al. 1993, 1997; Manz et al. 1991; Ott and Zober 1996; Zober et al. 1990). Most of the subjects in these studies were males working in chlorophenoxy herbicide or trichlorophenol manufacturing facilities. In one of the few studies assessing the carcinogenicity of 2,3,7,8-TCDD in women, Kogevinas et al. (1993) found a significantly elevated risk for cancer in women probably exposed to 2,3,7,8-TCDD during the production or application of chlorophenoxy herbicides and/or chlorophenols. The Zober et al. (1990), Fingerhut et al. (1991), Manz et al. (1991), Ott and Zober (1996) and Hooiveld et al. (1998) studies used current serum 2,3,7,8-TCDD levels in surviving workers to estimate exposure. The results of these studies, as well as two large multinational cohort mortality studies (Kogevinas et al. 1997; Saracci et al. 1991), are described below.

Saracci et al. (1991) examined cancer mortality in workers on the International Register of Workers Exposed to Phenoxy Herbicides and Their Contaminants. The registry consists of 18,390 workers (16,863 males and 1,527 females) distributed among 20 cohorts from 10 countries. Based on information obtained from questionnaires, factory or spraying records, and job histories, the workers were classified as exposed (13,482 workers), probably exposed (416), exposure unknown (541), or non-exposed (3,951). The exposed workers were workers who sprayed chlorophenoxy herbicides or worked in factories producing chlorophenoxy herbicides or chlorinated phenols. The probably exposed workers worked at facilities producing pentachlorophenol (145 workers) or 2,4-D, 2,4-(dichlorophenoxy)butanoic acid, (4-chloro-2-methyl-phenoxy)acetic acid, and (4-chloro-2-methyl)propanoic acid (275 workers). For 4 of the 20 cohorts, a minimum employment duration of 1 to 12 months was required for inclusion in the registry, for the remaining cohorts, the criterion for inclusion was “ever employed in production or spraying of phenoxy herbicides.” The average follow-up period for the entire cohort was 17 years. Cancer mortalities were not significantly increased in exposed and probably exposed workers (SMR=101; 95% CI=93–110). Duration of exposure or time since first exposure did not appear to influence the number of cancer deaths. The lack of both a clear definition of exposure and uniformity of exposure classification between and within cohorts makes the results difficult to interpret and lessens the confidence in the results.

After publication of the Saracci et al. (1991) study, the IARC cohort was expanded to include 12 manufacturing facilities in the United States (also examined by Fingerhut et al. 1991) and 4 plants in Germany (also examined by Becher et al. 1996). This expanded cohort, studied by Kogevinas et al. (1997), which included almost all workers world-wide who ever produced phenoxy herbicides, comprised 21,863 workers (20,851 males and 1,012 females) in 12 countries. 2,3,7,8-TCDD levels were measured in 573 workers at 10 facilities (approximately 50% of these workers were part of the NIOSH cohort examined by Fingerhut et al. 1991). The levels were 2-34 pg/g blood lipid (measured in 1990, mean not reported), 98–659 (1990, mean of 389 pg/g), 1.9–194 (1993, 53 pg/g), 3.0–131 (1988, 53.3 pg/g), 9–37 (1992, 17 pg/g), 1.3–6.49 (1996, estimated mean of 3.2 pg/g), 3–2,252 (1985–1994, estimated mean of 141 pg/g), 23–1,935 (1989–1992, estimated mean of 401.7 pg/g), and 2–3,400 (1987–1988, mean of 233 pg/g). Mortality rates for the cohort were compared to national mortality rates calculated using data from the WHO mortality data bank. There was a significant increase in the SMRs for all cancers for male workers (1,083 deaths; SMR=1.07; 95% CI=1.01–1.13) but not among female workers (44 deaths; SMR=0.93; 95% CI=0.68–1.25). When mortality rates were calculated for the 13,831 workers (males and females) exposed to phenoxy herbicides contaminated with 2,3,7,8-TCDD or higher chlorinated dioxins, the all-cancer SMR increased to 1.12 (710 deaths; 95% CI=1.04–1.21). The SMR for all cancer deaths was not elevated in workers not exposed to 2,3,7,8-TCDD or higher chlorinated dioxins. 2,3,7,8-TCDD-exposed workers were divided into groups based on years since first exposure, duration of exposure, and year of first exposure. The mortality rate appeared to be related to years since exposure and the related variable of year of first exposure. Significantly increased SMRs were observed in workers with a $20 year latency period (394 deaths; SMR=1.20; 95% CI=1.09–1.33), workers employed before 1955 (335 deaths; SMR=1.12; 95% CI=1.00–1.25), or workers employed between 1955 and 1964 (242 deaths; SMR=1.17; 95% CI=1.03–1.25), but these differences were overall small.

The cancer mortality experience of 247 male workers who were exposed to 2,3,7,8-TCDD during an accidental uncontrolled decomposition reaction and subsequent clean-up activities in a German 2,4,5-TCP production plant (BASF AG facility) in 1953 and followed for 34 years was studied by Zober et al. (1990). Three subcohorts were defined based on qualitative exposure information: Subcohorts 1 (n=69) included workers known to be exposed to 2,3,7,8-TCDD during the accident, and Subcohort 2 (n=84) and 3 (n=94) included workers considered exposed to amounts of 2,3,7,8-TCDD less than in Subcohort 1. Chloracne (114 cases) or erythema (13 cases) developed in 127 (51%) of the main cohort. Subcohorts 1, 2 and 3 contained 69 cases (21 severe, 27 extensive, 21 moderate), 17 cases (1 severe, 3 extensive, 13 moderate) and 28 cases (0 severe, 3 extensive, 25 moderate) of chloracne, respectively, and erythema affected 4 subjects in

Subcohort 2 and 9 subjects in Subcohort 3. Blood 2,3,7,8-TCDD levels were measured in 28 subjects in Subcohorts 1 (median 24.5 ppt, n=11), 2 (median 9.5 ppt, n=7), and 3 (median 8.4 ppt, n=10). Subjects with chloracne/erythema had higher average serum 2,3,7,8-TCDD levels (15 ppt, n=16) than those without (5.8 ppt, n=12). There was no clear increase in all malignant neoplasms or site-specific cancer in the entire cohort or either subcohort based on comparison with national mortality rates in the Federal Republic of Germany. When the 127 workers with chloracne/erythema were examined separately, the standardized mortality ratio (SMR) for all malignant neoplasms was not significantly elevated overall (SMR=139; 95% CI=87–211), although the SMR for all malignancies was significantly increased when analysis was restricted to workers whose first exposure was $20 years earlier (SMR=201; 95% CI=122–315, $p<0.05$).

In a follow-up to the Zober et al. (1990) study, the cohort of workers exposed at the BASF AG facility in Germany, was followed through 1992 (Ott and Zober 1996). The workers were divided into 3 subcohorts based on half-life extrapolated 2,3,7,8-TCDD body burdens of <0.01 µg/kg body weight, 0.1–0.99 µg/kg, and $1 µg/kg. 2,3,7,8-TCDD half-lives were estimated from repeated blood samples from 29 people with initial serum lipid 2,3,7,8-TCDD levels of 29–553 pg/g. The mean half-life was 5.8 years, but the half-life increased with higher percentages of body fat. Half-life estimates of 5.1 and 8.9 years were used for workers with 20 and 30% body fat, respectively. There was suggestive evidence that 2,3,7,8-TCDD exposure affected the occurrence of deaths from cancer (all sites combined) and deaths from respiratory or digestive cancer. The number of cancer deaths increased with increasing body burdens, SMRs of 0.8 (8 deaths; 95% CI=0.4–1.6), 1.2 (8 deaths; 95% CI=0.5–2.3), and 1.6 (15 deaths; 95% CI=0.9–2.6) in the cohorts with body burdens of <0.1, 0.1–0.99, and $1 µg/kg, respectively. No increases in cancer deaths were observed among nonsmokers; among current smokers, there were increases in cancer risks for workers with 2,3,7,8-TCDD body burdens of 1.0–1.99 µg/kg (6 deaths; SMR=3.0; 95% CI=1.1–6.5) and $2.00 µg/kg (6 deaths; SMR=4.0; 95% CI=1.5–8.6) but not for workers with lower 2,3,7,8-TCDD levels. Ott and Zober (1996) concluded that past body burdens of $1.0 µg/kg 2,3,7,8-TCDD were consistent with a 2,3,7,8-TCDD-induced carcinogenic effect. At the same time, they stated that with such a small cohort, the risk estimates are not very stable and could be affected by selection and confounding.

Becher et al. (1996) examined a cohort of 2,479 men employed at 4 German facilities involved in the production of phenoxy acid herbicides and chlorophenols. The workers were divided into 4 subcohorts: 1,144 male workers at facility 1 with a mean duration of employment of 7.7 years, 135 male workers at facility 2 with a mean duration of employment of 21.5 years, 520 male workers at facility 3 with a mean duration of employment of 9.1 years, and 680 workers at facility 4 with a mean duration of employment of

18.5 years. 2,3,7,8-TCDD blood levels in groups of workers in subcohorts 1 (112 males and 18 females) and 2 (8 workers, all with a history of chloracne) were 3–2,252 and 163–1,935 pg/g blood lipid, respectively. The study authors noted that 2,3,7,8-TCDD exposure was probably lower in subcohorts 3 and 4 because 2,3,7,8-TCDD-contaminated products only made up a small percentage of the total products manufactured at these facilities. Messerer et al. (1998) measured serum CDD and CDF levels in 19 of the current employees at facility 4. The mean CDD and CDF levels were slightly higher than background levels, even in the most exposed workers (involved in synthesis); the mean 2,3,7,8-TCDD and TEQ levels in the 7 synthesis workers were 3.8 and 35.4 ppt, respectively, as compared to 3.2 and 25.0 ppt in controls. The SMR for all cancer mortalities was significantly increased in the entire cohort (138 deaths; SMR=119; 95% CI=100–141); subcohort 1 was the only subcohort with a significant increase in all cancer mortalities (97 deaths; SMR=134; 95% CI=109–164). When the entire cohort was divided into groups based on time since first exposure, there were no increases in SMRs for all cancer deaths during the three time periods (0 to <10 years, 10 to <20 years, and $20 years).

In the Fingerhut et al. (1991) study, cancer mortality was evaluated in 5,172 male workers involved in the production of 2,3,7,8-TCDD-contaminated chemicals in 12 U.S. plants, as well as in subcohorts with low (<1 year, n=1,516) or high ($1 year, n=1,520) exposures and $20 years latency. Exposure was documented by reviewing job descriptions and records of 2,3,7,8-TCDD levels in industrial hygiene samples, and measuring lipid-adjusted serum 2,3,7,8-TCDD levels in 253 of the workers from two of the facilities; it was assumed that a similar relationship would exist at the other 10 facilities. Duration of exposure was used as a surrogate for cumulative 2,3,7,8-TCDD exposure on the basis of a high correlation ($r=0.72$, $p<0.001$) between log serum 2,3,7,8-TCDD level and log number of years of exposure. Mean lipid-adjusted serum 2,3,7,8-TCDD levels were 233 ppt (range 2–3,400) for all 253 workers, 418 ppt for 119 workers with $1 year exposure and 7 ppt in a comparison group of 79 unexposed persons. When compared to the U.S. population, mortality from all cancers was significantly increased ($p<0.05$) in the overall cohort (SMR=115; 95% CI=102–130) and the high exposure subcohort (SMR=146; 95% CI=121–176). Cancer mortality increased with increasing latency. The number of deaths were too small to allow meaningful analysis according to duration of exposure.

A cancer mortality follow-up study of 1,583 workers (1,184 men, 399 women) who were employed in a German chemical plant that produced trichlorophenol, 2,4,5-T, and other herbicides known to be contaminated with 2,3,7,8-TCDD and other polychlorinated dioxins and furans (this appears to be the same facility as subcohort 1 in the Becher et al. [1996] study) was reported by Manz et al. (1991). Production of

these chemicals was discontinued during 1954–57 after an outbreak of chloracne. Cohort members worked for at least 3 months during 1952–1984 and were followed through 1989. SMRs were calculated using national mortality rates for West Germany and deaths in a cohort of male gas supply company workers. Exposures of cohort members were classified as high (n=496), medium (n=901), or low (n=186) based on an analysis of production processes in the plants where they had worked. Some validation for these categories was provided by measurement of adipose 2,3,7,8-TCDD levels in 48 males in 1985 (mean concentrations were 296 ng/kg lipid in 37 subjects in the high-exposure group compared with 83 ng/kg for 11 subjects in the medium- and low-exposure groups combined). When compared with national rates, mortality from all cancers combined was increased in the entire cohort (93 deaths, SMR=1.24; 95% CI=1.00–1.52), especially among men in the high exposure subgroup with $20 years employment (8 deaths, SMR=2.54; 95% CI=1.00–5.00) or who began employment before 1955 (18 deaths, SMR=2.11; 95% CI=1.25–3.34). The greatest increase in risk was found in high exposure men with time of entry before 1955 and $20 years employment (8 deaths, SMR=3.5; 95% CI=1.51–6.9). The aforementioned findings were corroborated when the gas workers were used as the comparison group. In a follow-up study (Flesch-Janys et al. 1998) in which the cohort was followed through 1992, the SMR for all cancers was 1.4 (124 deaths; 95% CI=1.17–1.68). When the workers were divided into four exposure groups, a significant increase in SMR (36 deaths; SMR=1.73; 95% CI=1.21–2.40) was only found in the highest exposure group (2,3,7,8-TCDD levels of $2,503 ng/kg blood lipid × years, a measure of cumulative lifetime exposure); the trend toward increasing SMR with increasing dose was also statistically significant.

The cohort in the Manz et al. (1991) study served as the basis for additional analysis by Flesch-Janys et al. (1995, 1998), who investigated the relation between mortality and quantitative measure of PCDD/F exposure. The male chemical workers (n=1,177) were followed for an additional 3 years. Blood levels of each PCDD/F congener at the end of exposure were estimated for all members of the cohort based on work histories (durations of exposure in particular departments) and tissue levels from a subgroup of male workers, and assuming one-compartment first-order elimination kinetics. A total TEQ level was also estimated for all measured CDDs and CDFs combined as the weighted sum of PCDD/F congeners using toxicity equivalent factor (TEF) values (see Section 2.5 for a detailed explanation on TEFs and dioxin equivalents). In the Flesch-Janys et al. (1995) study, risk ratios for the cohort were estimated with year-of-birth stratified Cox regression using seven exposure levels (the reference cohort, the first four quintiles and the ninth and tenth deciles of the estimated 2,3,7,8-TCDD levels and total TEQ); an external cohort of gas supply workers (n=2,158) served as an unexposed control group. The estimated mean 2,3,7,8-TCDD level for the entire cohort at the end of employment in the plant was 141.4 ng/kg blood fat (median of 38.2 ng/kg).

The estimated mean total dioxin equivalents, calculated as the weighted sum of combined PCDD/F congeners, was 296.5 ng/kg (median of 118.3 ng/kg). There was a dose-dependent increase in cancer mortality with increasing levels of 2,3,7,8-TCDD (p=0.01 for trend), predominantly due to increased risk ratio (3.30; 95% CI=2.05–5.31) in the highest-dose group (344.7–3,890.2 ng/kg). Similar findings were obtained when total TEQs were used as the exposure parameter, or when the two lowest-dose groups in the chemical-worker cohort were combined and used for reference. In the Flesch-Janys et al. (1998) study, the mean blood 2,3,7,8-TCDD level in the subgroup (blood or adipose tissue samples collected from 236 males) was 108.3 ng/kg blood lipid (range, 2.0–2252 ng/kg), the mean TEQ for CDD/F congeners was 247.5 ng/kg (11.7–2,985.8), and the mean TEQ without 2,3,7,8-TCDD was 184.0 ng/kg (9.7–1,263.4 ng/kg). When the workers were divided into groups based on cumulative TEQ exposure, statistically significant SMRs were found in the second (TEQ between 360.9 and 1,614.4 ng/kg × years) and fourth (TEQ greater than 5,217.7 ng/kg × years) quartiles; SMRs of 1.64 (34 deaths; 95% CI=1.13–2.29) and 1.64 (34 deaths; 95% CI=1.13–2.29), respectively. A significant relationship between cumulative TEQ level and SMR for all cancer was not found. Potential sources of error and bias in this study include lack of random sampling in the subgroup with PCDD/F assays and the assumption of first-order elimination kinetics. Flesch-Janys et al. (1998) compared age of employment and years spent in each product department for workers with measured 2,3,7,8-TCDD blood levels and workers without blood level data and found no major differences between the two groups.

Workers at two Dutch phenoxy herbicide and chlorophenols production facilities comprised the cohort for the Bueno de Mesquita et al. (1993) study of cancer mortality. The cohorts consisted of any worker employed between 1955 and 1985 (facility A) or between 1965 and 1986 (facility B). An industrial accident at facility A resulted in a release of CDDs, including 2,3,7,8-TCDD. Mortality rates in the workers were compared to national rates. In workers at facility A, there was a slight increase in deaths from all cancers; however, the increase was not statistically significant (26 deaths; SMR=118; 95% CI=77–173); the SMR for all cancers was not increased at facility B or in the combined entire cohort. Likewise, dividing the workers at each facility into groups based on time since first exposure or duration of exposure did not result in any significant increases in SMRs. Hooiveld et al. (1998) followed the workers at facility A for another 6 years. Additionally, serum levels of CDDs, CDFs, and PCBs were measured in a sample of 47 surviving workers who were employed for at least 1 year and whose date of first employment was prior to 1975; 14 of these workers were exposed during the accident, 17 were workers not involved in the accident, and 16 were not exposed to phenoxy herbicides or chlorophenols. The average 2,3,7,8-TCDD serum levels were 105.2, 42.9, 16.6, and 7.6 ppt (lipid adjusted) in the accident-exposed workers with a history of chloracne (12 workers),

accident-exposed workers without chloracne (2 workers), nonaccident-exposed workers, and nonexposed workers, respectively; the mean serum 2,3,7,8-TCDD levels at the time of maximum exposure (extrapolated levels) were estimated at 2,014.4, 806.6, and 244.1 ppt in the accident-exposed workers with a history of chloracne, accident-exposed workers without chloracne, and nonaccident-exposed workers, respectively. There was an increase in deaths from all cancers among all exposed workers (51 deaths; SMR=1.5; 95% CI=1.1–1.9), as compared to national rates; a slightly higher mortality rate (20 deaths; SMR=1.7; 95% CI=1.1–2.7) was observed in the subcohort of accident-exposed workers. When nonexposed workers were used as a comparison group, the relative risk of all cancer deaths was 4.1 (51 deaths; 95% CI=1.8–9.0), the relative risk was adjusted for age, calendar year at end of follow-up, and time since first exposure/ employment. When the workers were divided into three groups based on model-predicted 2,3,7,8-TCDD levels, the relative risk of all cancer deaths was elevated in workers with medium or high exposure, as compared to workers with low exposure (adjusted RR=4.8; 95% CI=2.0–11.3 for the medium exposure group and adjusted RR=4.4; 95% CI=1.9–10.4 for the high exposure group).

Case-control studies have been designed to determine if 2,3,7,8-TCDD exposure results in increased risks for site-specific cancers. Case-control studies have found significant increases in the risk of soft-tissue sarcomas in Swedish agricultural, forestry, and horticultural workers (Eriksson et al. 1981, 1990; Hardell and Eriksson 1988; Hardell and Sandstrom 1979), workers involved in manufacturing and application of phenoxy herbicides (Kogevinas et al. 1995), and New Zealand farmers (Smith et al. 1984a). In the Eriksson et al. (1990) study, the risk ratio of soft-tissue sarcoma was 1.80 (95% CI=1.02–3.18) in subjects exposed to phenoxyacetic acid herbicides and/or chlorophenols. In subjects exposed to phenoxyacetic acid herbicides only or chlorophenols only, the risk ratios were 1.34 (95% CI=0.7–2.56) and 5.25 (95% CI=1.69–16.34), respectively. When the phenoxyacetic acid herbicide-only subjects were divided into two groups of subjects predominantly exposed to 2,4,5-T and those exposed to phenoxyacetic acid herbicides other than 2,4,5-T, risk ratios of 1.81 (95% CI=0.85–3.87) and 0.60 (95% CI=0.18–2.06), respectively, were calculated. Hardell et al. (1995) conducted a meta-analysis of their four Swedish case-control studies (Eriksson et al. 1981, 1990; Hardell and Eriksson 1988; Hardell and Sandstrom 1979). The odds ratios for workers exposed to phenoxyacetic acid herbicides or chlorophenols, phenoxy herbicides only, or chlorophenols only were 2.8 (90 cases; 95% CI=2.1–4.4), 2.7 (59 cases; 95% CI=1.9–4.7), and 3.3 (34 cases; 95% CI=1.8–6.1), respectively. The data from this study suggest that the increased possible risks of soft-tissue sarcomas observed in phenoxy herbicide and chlorophenols applicators may be due to exposure to the 2,3,7,8-TCDD (or other CDDs) contamination of the mixture. However, the results of the Kogevinas et al. (1995) study suggest that the possible risk of soft-tissue sarcoma may not be specific to 2,3,7,8-TCDD-contaminated

phenoxy herbicides. An increase in the possible risk of soft-tissue sarcoma (OR of 10.3; 95% CI=1.2–90.6) was found in multinational workers involved in the production and spraying of phenoxy herbicides (Kogevinas et al. 1995). Exposure to chlorophenols was not associated with an increase in the possible risk of soft-tissue sarcomas (OR=1.29; 95% CI=0.24–6.91). Using job histories, the workers were divided into groups based on the type of phenoxy herbicide used. Excess possible risks of soft-tissue sarcoma were observed in workers predominantly exposed to 2,4-dichlorophenoxyacetic acid (2,4-D, OR=5.7; 95% CI=1.1–29), 2,4,5-T (OR=4.3, 90% CI=0.7–26), 4-chloro-2-methylphenoxyacetic acid (MCPA, OR=11.3; 95% CI=1.3–98), exposure to any CDDs or CDFs (OR=5.6; 95% CI=1.1–28), and exposure to 2,3,7,8-TCDD (OR=5.2, CI=0.9–32). Although this study suggests that exposure to 2,3,7,8-TCDD increases the possible risk of soft-tissue sarcoma, it also suggests that exposure to phenoxy herbicides on their own may also increase the possible risk of soft-tissue sarcoma.

Cohort mortality studies have also found increases in the incidences of soft-tissue sarcomas. Fingerhut et al. (1991) found significant increase in deaths from soft-tissue sarcomas (SMR=922; 95% CI=190–2,695) in the high-exposure cohort, although this was only based on 3 deaths. In the Saracci et al. (1991) multinational cohort, an increase in deaths from soft-tissue sarcoma was observed in phenoxy herbicide sprayers (3 deaths, SMR=297; 95% CI=61–868) and in workers dying 10–19 years after first exposure (4 deaths, SMR=606; 95% CI=165–1,552). Similarly, the Kogevinas et al. (1997) study of the IARC cohort found 3 cases of soft-tissue sarcoma in workers exposed for 10–19 years (SMR=6.52; 95% CI=1.35–19.06); shorter exposure durations did not result in significantly elevated SMRs. Additionally, when workers were divided into latency groups, the SMRs were not elevated. Duration of probable exposure to 2,3,7,8-TCDD did not appear to influence soft tissue sarcoma cancer risks.

Case-control studies and/or cohort mortality studies have also found significant increase in the possible risk of malignant lymphoma (RR=4.8; 95% CI=2.9–8.1) in Swedish agricultural, forestry, and horticultural workers Hardell et al. 1981) and German phenoxy herbicide and chlorophenols manufacturer workers (SMR=239; 95% CI=119–427) (Becher et al. 1996); non-Hodgkin's lymphoma in Wisconsin farmers (OR=1.22; 95% CI=0.98–1.51) (Cantor 1982), multinational phenoxy herbicide manufacturers and applicators (OR of 1.25; CI=0.54–2.90) (Kogevinas et al. 1995), and German workers at a phenoxy herbicide and chlorophenols facility (SMR=375; 95% CI=101–957) (Becher et al. 1996); and stomach cancer in railroad workers (rate ratio of 6.1) (Axelson et al. 1980) and workers at a German trichlorophenol facility (observed/expected ratio of 3/0.52) (Thiess et al. 1982).

Cohort mortality studies by Fingerhut et al. (1991), Zober et al. (1990), Manz et al. (1991) (including the Flesch-Janys et al. [1998] follow-up data), and Kogevinas et al. (1997) found significant increases in risk of respiratory tract cancer. In the Manz et al. (1991) study, a slightly increased risk of lung cancer was observed in the entire cohort compared to the risk in the West German population (30 deaths, SMR=1.41; 95% CI=0.95–2.01) or the reference gas workers (26 deaths, SMR=1.67; 95% CI=1.09–2.44); the increase in lung cancer risk was statistically significant when the gas workers were used as the referent group (Manz et al. 1991). Smoking does not appear to be a major confounder because available data (partial cohort) suggest that the percentage of smokers in the study cohort and gas-worker control group were similar. In the Flesch-Janys et al. (1998) follow-up of this cohort, the SMRs for lung (38 deaths) and respiratory (44 deaths) cancer were 1.51 (95% CI=1.07–2.08) and 1.71 (95% CI=1.24–2.29), respectively. When the cohort was divided into four cumulative exposure categories, the SMRs were not significantly elevated for any exposure group. In this cohort, blood 2,3,7,8-TCDD levels were not correlated with smoking status (Flesch-Janys et al. 1995). The study authors additionally noted that when lung cancer deaths were removed from total cancer deaths, there was a stronger relationship between 2,3,7,8-TCDD levels and cancer rates, suggesting that smoking was not a strong confounder. Death from cancers of the respiratory tract (SMR=142; 95% CI=103–192) were significantly increased in the high-exposure subcohort of the Fingerhut et al. (1991) study. The expected number of lung cancers was adjusted for smoking using smoking-prevalence data for a small subset of workers; the adjusted SMR for the high-exposure subcohort was 137 (95% CI=98–187). The authors concluded that the increased lung cancer risk was probably not due to smoking because the incidences of smoking-related diseases were not higher than expected in the subcohort and mortality from non-malignant respiratory disease was lower than expected. However, when smoking was included as a confounding factor, the increased risk for lung cancer was no longer statistically significant. Zober et al. (1990) found a borderline increase in mortality from cancer of the trachea bronchus/ lung (SMR=252; 95% CI=99–530) in workers with chloracne/erythema and $20 years latency. In the follow-up to the Zober et al. (1990) study, Ott and Zober (1996) found an increased number of deaths from respiratory cancer in the subcohort with 2,3,7,8-TCDD body burdens of $1 µg/kg (SMR=2.4; 95% CI=1.0–5.0). However, in 10 of the 11 cases, the worker smoked, which makes it difficult to determine if the cancer deaths were due to 2,3,7,8-TCDD exposure. The Kogevinas et al. (1997) examination of the expanded IARC cohort did not find a significant elevation in deaths from lung cancer (225 deaths; SMR=1.12; 95% CI=0.98–1.28) among workers exposed to phenoxy herbicides contaminated with 2,3,7,8-TCDD or higher chlorinated dioxins, but it did find a rise in deaths from other respiratory organ cancers (9 deaths; SMR=3.20; 95% CI=1.46–6.08).

Using regression analysis based on Cox's proportional hazards model, Ott and Zober (1996) found evidence of association between 2,3,7,8-TCDD exposure and digestive cancer (conditional risk ratio of 1.46; 95% CI=1.13–1.89); the primary tumor sites were the liver, stomach, and pancreas.

A number of studies have looked at cancer incidences among Vietnam veterans to determine if exposure to Agent Orange with its 2,3,7,8-TCDD contamination resulted in a higher cancer risk. Many of these studies compared cancer incidences in Vietnam veterans to Vietnam-era veterans stationed outside of Vietnam. A limitation of this study design is that not all veterans in Vietnam were exposed to Agent Orange and exposure was lower than that of occupational workers. CDC (1988) found that the levels of 2,3,7,8-TCDD in Vietnam veterans were usually similar to a comparison group. Thus, studies which examined cancer incidences in "Vietnam veterans" may not be adequate to assess the carcinogenicity of 2,3,7,8-TCDD. Wolfe et al. (1985) focused on Air Force personnel involved in Operation Ranch Hand. 2,3,7,8-TCDD levels in 888 Ranch Hand personnel was 12.4 ppt as compared to 4.2 ppt in a referent group of Air Force personnel (CDC 1987; USAF 1991). No significant alterations in the incidence of systemic malignancies were observed in the Ranch Hand personnel, as compared to a group of veterans flying cargo in Southeast Asia during the Vietnam war. A significant increase in non-melanomic skin cancer (predominantly basal cell carcinoma) was found in the Ranch Hand personnel; however, cancer incidences were not adjusted for sun exposure. No significant alterations in systemic malignancy indices were found. In a similar study of Air Force veterans involved in Operation Ranch Hand, a significant increase in benign systemic neoplasms was observed (USAF 1991). No alterations in the risk of malignant neoplasm were observed. No increases in the risk of Hodgkin's disease, non-Hodgkin's lymphoma or soft-tissue sarcoma were observed; however, the statistical power of the study to detect significant risk ratios for site-specific cancers was limited by the small number of cancers and the small sample size. The incidence of benign neoplasms (primarily lipomas) was highest in veterans with the highest blood dioxin levels. The incidence of basal cell skin neoplasms was not positively associated with serum dioxin levels except among enlisted flyers with basal cell carcinomas at sites other than the ear, face, head, or neck.

Increases in the risk of several types of cancer have been observed in residents of Seveso, Italy. In the residents with the highest exposure (zone A), no increases in the risk ratio of all malignancies were observed (Bertazzi et al. 1993). However, the small number of zone A residents (724) limits the statistical power of the analysis. Among residents living in zone B (4,824 people), significant increases were observed for the risk of hepatobiliary cancer (risk ratio of 3.3; 95% CI=1.3–8.1) and multiple myeloma (risk ratio of 5.3; 95% CI=1.2–22.6) in women and lymphoreticulosarcoma in men (RR of 5.7; 95% CI=1.7–19). In zone R

(31,647 residents), the risk ratio of soft-tissue sarcomas in men (2.8; 95% CI=1–7.3) was significantly increased. In both zone B and R, the risk ratios of all malignancies was not significantly altered. Estrogen-dependent cancers (breast cancer and corpus uteri cancer) were consistently decreased in the women living in zone A, B, and R. It should also be noted that the latency period of 10 years may be too short to find increases in other types of cancer. A study of children (aged 0–19 years at the time of the accident) exposed to 2,3,7,8-TCDD during the accident in Seveso found increased risks of Hodgkin's lymphoma [RR =2; 95% CI=0.5–7.6), myeloid leukemia (RR=2.7; 95% CI=0.7–11.4), and thyroid cancer (RR=4.6; 95% CI=0.6–32.7) (Pesatori et al. 1993). However, the differences in RRs for these cancer types between the Seveso residents and the control population did not reach statistical significance. The small number of detected cancers and the relatively short latency period (10 years) limits the interpretation of the results of this study. Similar results were found in the 15-year follow-up study (Bertazzi et al. 1997). No significant increases in cancer mortality were found in zone A residents (805 residents, 70 deaths). In zone B, death from all cancers was not significantly elevated in males (104 deaths; RR=1.1; 95% CI=0.9–1.3) or females (48 deaths; RR=0.9; 95% CI=0.7–1.2). However, significant increases in site-specific cancers were observed, including rectal cancer in males (7 deaths; RR=2.9; 95% CI=1.2–5.9), pleural cancer in males (31 deaths; RR=5.3; 95% CI=1.1–5.5), lymphohemopoietic cancer in males (12 deaths; RR=2.4; 95% CI=1.2–4.1), leukemia in males (7 deaths; RR=3.1; 95% CI=1.3–6.4), and myeloma in females (4 deaths; RR=6.6; 95% CI=1.8–16.8). The cancer with an elevated incidence among zone R residents was bone cancer in females (7 deaths; RR=2.4; 95% CI=1.0–4.9).

The available epidemiology data suggest that 2,3,7,8-TCDD may be a human carcinogen. Statistically significant increases in risks for all cancers were found in highly exposed workers with longer latency periods. Although the estimated SMRs are low, they are consistent across studies with the highest exposures. The evidence for site-specific cancers is weaker, with some data suggesting a possible relationship between soft-tissue sarcoma, non-Hodgkin's lymphoma, or respiratory cancer with 2,3,7,8-TCDD exposure. It should be emphasized that some of the human studies do not provide adequate exposure data and were confounded by concomitant exposure to other chemicals.

2,3,7,8-TCDD body burdens calculated from available serum lipid 2,3,7,8-TCDD levels are presented in Table 2-1.

2.2. ANIMAL STUDIES

This section contains descriptions and evaluations of studies and presents levels of significant exposure for CDDs based on toxicological studies.

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, developmental, reproductive, 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers 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 (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of CDDs are indicated in Tables 2-2, 2-3, and 2-4 and Figures 2-1 and 2-2.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made (see Section 2.5), where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989c), 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.

2.2.1 Inhalation Exposure

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

2.2.1.1 Death

2.2.1.2 Systemic Effects

2.2.1.3 Immunological Effects

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in animals after inhalation exposure to CDDs.

2.2.2 Oral Exposure

Information regarding adverse health effects in animals exposed to CDDs via the oral route was located for the following congeners: 2-monochlorodibenzo-*p*-dioxin (2-MCDD), 2,3-dichlorodibenzo-*p*-dioxin (2,3-DCDD), 2,7-dichlorodibenzo-*p*-dioxin (2,7-DCDD), 1,2,3-trichlorodibenzo-*p*-dioxin (1,2,3-TrCDD), 1,2,3,4-tetrachlorodibenzo-*p*-dioxin (1,2,3,4-TCDD), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (1,2,3,7,8-PeCDD), 1,2,3,4,7,8-hexachloro-dibenzo-*p*-dioxin (1,2,3,4,7,8-HxCDD), 1,2,4,7,8-pentachlorodibenzo-*p*-dioxin (1,2,4,7,8-PeCDD),

1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (1,2,3,6,7,8-HxCDD), 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (1,2,3,7,8,9-HxCDD), 1,2,3,4,6,7,8,-heptachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8,-HpCDD), and 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin (OCDD). Some of the animal studies used a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD. Of all the CDD congeners, 2,3,7,8-TCDD has been the one most extensively studied.

2.2.2.1 Death

Numerous studies provided doses associated with death following exposure to CDDs in animals. LD_{50} (lethal dose, kill for 50% of dosed animals during a certain time interval) values for each congener varied not only among species, but also among different strains.

LD_{50} values following a single oral dose of 2,3,7,8-TCDD were calculated as 22 µg/kg (males) and 45 µg/kg (females) in Sherman rats (Schwetz et al. 1973); and 164 µg/kg, 297 µg/kg, 303 µg/kg, and 340 µg/kg in Fischer 344 rats from Charles River Breeding Laboratories, Charles River CD, Frederick Cancer Research Center, and Harlan Industries, respectively (Walden and Schiller 1985); 165 µg/kg (males) and 125 µg/kg (females) in Osborne Mendel rats (NTP 1982b); 43 µg/kg in male Sprague-Dawley rats (Stahl et al. 1992), and 60 and 100 µg/kg in female and male Long Evans rats, respectively (Fan and Rozman 1995). A single gavage dose of 100 µg/kg caused death in 95% of exposed male Fischer 344 rats (Kelling et al. 1985), and a dose of 25 µg/kg led to the death of 25% of exposed male Sprague-Dawley rats (Seefeld et al. 1984a). Furthermore, the reported LD_{50} values were 4.2 µg/kg in minks (Hochstein et al. 1988), 115 µg/kg in New Zealand albino rabbits (Schwetz et al. 1973b), 1.75 µg/kg in male Hartley guinea pigs (McConnell et al. 1984), 0.6 µg/kg (males) and 2.1 µg/kg (females) in Hartley guinea pigs (Schwetz et al. 1973b), and 1,157 µg/kg (Olson et al. 1980a) or 5,051 µg/kg (Henck et al. 1981) in Syrian hamsters. A 42-day LD_{50} of 2.5 µg/kg was calculated for female Hartley guinea pigs when 2,3,7,8-TCDD was administered in corn oil and 19 µg/kg when administered in methyl cellulose (Silkworth et al. 1982). No effect on survival was observed after a single oral dose of 200 µg/kg in B6C3F_1 mice (NTP 1982b), but 69% of C57BL/6 mice died following exposure to 360 µg/kg (Kelling et al. 1985), and an LD_{50} was calculated as 146 µg/kg 2,3,7,8-TCDD in male C57BL mice (Smith et al. 1981). An acute LD_{50} in excess of 3,000 µg/kg was reported for male DBA/2J mice (Weber et al. 1995). Increased lethality was observed in Hartley guinea pigs exposed to 0.03 µg/kg/day 2,3,7,8-TCDD in the feed for 11 days (DeCaprio et al. 1986) and in pregnant rabbits following 10 daily doses of 1 µg/kg during gestation (Giavini et al. 1982). Beagle dogs survived a single dose of 300 µg/kg but not 3,000 µg/kg (Schwetz et al. 1973). In addition, 3 of 12 pregnant rhesus

monkeys died following a single dose of 1 µg/kg (McNulty 1984). It is evident from the above results that guinea pigs were the most sensitive species, while hamsters were the most resistant (up to 5,000 times greater lethal doses). In all studies cited above, the animals died following a latency period of several days (mean values varied from 9 to 43). In almost all laboratory animals, a pronounced wasting syndrome appears to be a major contributor to lethality.

In the intermediate-duration experiments, increased lethality was observed in Osborne Mendel rats exposed to 2,3,7,8-TCDD by gavage in oil vehicle at 0.56 µg/kg/day for up to 13 weeks (NTP 1982b). Mortality of 5% (no deaths in controls) was observed in Sprague-Dawley rats administered 2,3,7,8-TCDD by gavage at a rate of approximately 0.8 µg 2,3,7,8-TCDD/kg/day for 13 weeks (Viluksela et al. 1994); the first death occurred on day 57. Four of 7 male Sprague-Dawley rats dosed by gavage with approximately 1.6 µg 2,3,7,8-TCDD/kg/day died in a 10-week study (Li and Rozman 1995); the mean time to death was 53.5 days. Increased mortality was reported in Hartley guinea pigs exposed daily for up to 60 days to diets that provided 0.03 µg/kg/day (DeCaprio et al. 1986); 4 of 10 males died by day 42 and 4 of 10 females by day 59. In a dietary study, all male Sprague-Dawley rats that received the diet that provided the highest doses (3.4 µg/kg/day or more) died within 4 weeks (Van Miller et al. 1977). C57BL/6 mice had decreased survival following exposure by gavage to 3 µg/kg/day of 2,3,7,8-TCDD 3 days a week for 25 weeks (Umbreit et al. 1987). Two monkeys were exposed intermittently by gavage to 0.6 µg/kg/day of 2,3,7,8-TCDD for 3 weeks and both died (McNulty 1984); 5 of 8 monkeys died within 2 months following exposure to diets that provided 0.02 µg/kg/day (Hong et al. 1989); also, 5 of 8 monkeys died within 9 months of dietary exposure to 0.011 µg/kg/day (Allen et al. 1977). In all species, severe weight loss and body fat depletion were experienced prior to death, but usually no other overt toxic signs were observed. Pancytopenia, a secondary effect, was the cause of death in monkeys.

Decreased survival was reported after chronic exposure to CDDs. Chronic dietary exposure to 2,3,7,8-TCDD increased the mortality over controls in Sprague-Dawley rats at 0.1 µg/kg/day (Kociba et al. 1978a). Increased mortality also occurred in Swiss mice given 2,3,7,8-TCDD by gavage at 1.0 µg/kg/day (Toth et al. 1979) and in $B6C3F_1$ mice at 0.36 µg/kg/day (Della Porta et al. 1987). In both studies, the mice were dosed once a week for 1 year and followed for the rest of their lives or until 110 weeks of age. No treatment-related effects on survival were observed in Osborne-Mendel rats or in $B6C3F_1$ mice administered up to 0.25 µg 2,3,7,8-TCDD/kg/day, 2 days a week by gavage for 104 weeks(0.071 µg/kg/day for rats and male mice; 0.3 µg/kg/day for female mice) (NTP 1982b).

Increased mortality occurred after acute exposure to other congeners. After a single oral dose of a mixture of 1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD, LD_{50} values were calculated as 1,800 µg/kg and 800 µg/kg in male and female Osborne-Mendel rats, respectively, and 750 µg/kg and 500 µg/kg in male and female $B6C3F_1$ mice, respectively (NCI/NTP 1980). In addition, LD_{50} values were calculated for several congeners in guinea pigs (29,444 µg/kg for 1,2,3-TrCDD, 1,125 µg/kg for 1,2,4,7,8-PeCDD, 3.1 µg/kg for 1,2,3,7,8-PCDD, 70–100 µg/kg for 1,2,3,6,7,8-HxCDD, 60–100 µg/kg for 1,2,3,7,8,9-HxCDD, and 72.5 µg/kg for 1,2,3,4,7,8-HxCDD) and in mice (825 µg/kg for 1,2,3,4,7,8-HxCDD and 337.5 µg/kg for 1,2,3,7,8-PCDD) following a single oral exposure by gavage in oil vehicle (McConnell et al. 1978b). In male Sprague-Dawley rats, the oral LD_{50} for 1,2,3,7,8-PCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD administered in corn oil/acetone (95/5) was 206, 887, and 6,325 µg/kg, respectively (Stahl et al. 1992). Other CDD congeners have a much lower order of toxicity, as evidenced by data showing no effects on mortality at much higher doses than those of 2,3,7,8-TCDD, TrCDD, HxCDD, or PCDD that cause death. No deaths were observed after a single oral dose of 1×10^6 and 2×10^6 µg/kg 2,7-DCDD in Sprague-Dawley rats and Swiss Webster mice, respectively (Schwetz et al. 1973). In addition, rats and mice survived acute oral doses of 1×10^6 and 4×10^6 µg/kg OCDD, respectively (Schwetz et al. 1973). The relative species differences in sensitivity for 2,3,7,8-TCDD also applied for other congeners.

Mortality rates of 15 and 50% were reported in groups of male Sprague-Dawley rats administered 73 and 110 µg 1,2,3,4,6,7,8-HpCDD/kg/day by gavage for 13 weeks, respectively (Viluksela et al. 1994). At the highest dose, the first death occurred on day 31; at the 73 µg/kg/day dose, on day 41. Fifteen out of 20 female Sprague-Dawley rats died during a 13-week treatment period with daily doses of approximately 2.6 µg 1,2,3,7,8-PeCDD/kg (total dose was 233 µg/kg) (Viluksela et al. 1998a). The first death occurred on day 16. The same mortality rate was observed in males treated with approximately 3.8 µg/kg/day (total dose was 350 µg/kg). In the same study, administration of approximately 10.3 µg 1,2,3,4,7,8-HxCDD resulted in a 25% death rate (5/20, first death on day 61) in female rats; the same death rate was seen among male rats treated with approximately 15.4 µg/kg/day (first death on day 24). The main causes of death were wasting syndrome, hemorrhage, and anemia (Viluksela et al. 1998a). No effects on survival were observed following chronic dietary exposure of Osborne-Mendel rats and $B6C3F_1$ mice to 5×10^5 µg/kg/day of 2,7-DCDD and to 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively (NCI/NTP 1979a), or following chronic gavage dosing with a mixture of 1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD at 0.34 µg/kg/day and 0.7 µg/kg/day, respectively (NCI/NTP 1980).

In conclusion, 2,3,7,8-TCDD was the most toxic of all congeners tested, and doses on the order of several µg/kg body weight have led to death in all species tested, except hamsters and dogs, in acute-exposure experiments. In contrast, of the congeners tested, 2,7-DCDD and OCDD were the least toxic as tested animals survived very high doses (g/kg body weight). The wasting syndrome was the major toxic effect of acute- and intermediate-duration exposure to CDDs in most species. It was characterized by body weight loss, adipose tissue depletion, and eventual death. In most of the chronic duration studies the cause of death was not determined.

The LD_{50} values and all reliable representative LOAEL values for death in each species and duration category for each congener tested are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable representative LOAEL values for each systemic effect in each species and duration category for each congener tested are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

Respiratory Effects. Few studies have examined the respiratory system in animals following oral exposure to CDDs. However, serious respiratory effects have been observed in monkeys that died from 2,3,7,8-TCDD exposure.

Bleeding from the nose was reported in rhesus monkeys exposed via gavage to 0.1 µg/kg/day, 3 days a week for 3 weeks (McNulty 1984). Hemorrhage, hyperplasia, and metaplasia of the bronchial epithelium (as well as at other organ sites that had mucous-secreting cells) developed in monkeys exposed to diets providing 0.011 µg/kg/day for 9 months (Allen et al. 1977); 5 of 8 monkeys died with this dose level. Focal alveolar hyperplasia and squamous metaplasia and carcinoma were reported in Sprague-Dawley rats chronically exposed to 0.1 µg/kg/day 2,3,7,8-TCDD in the feed (Kociba et al. 1978a). Since powdered feed containing 2,3,7,8-TCDD was given to the rats, there is a distinct possibility that the respiratory effects were attributable to inhalation exposure rather than oral systemic absorption. In contrast, no respiratory effects were observed in rats or mice chronically exposed by gavage to 2,3,7,8-TCDD at approximately 0.071 µg/kg/day or 0.3 µg/kg/day, respectively (NTP 1982b).

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Monkey (Rhesus)	once (GO)				70 (1/3 died)	McConnell et al. 1978
2	Monkey (Rhesus)	once (GO)				1.0 (3/12 dams died)	McNulty 1984
3	Rat (Long- Evans)	once (GO)				60 F (LD_{50})	Fan and Rozman 1995
4	Rat (Fischer- 344)	once (GO)				100 M (95% died)	Kelling et al. 1985
5	Rat (Osborne-Mendel)	once (GO)				165 M (LD_{50})	NTP 1982b
						125 F (LD_{50})	
6	Rat (Sherman)	once (GO)				22 M (LD_{50})	Schwetz et al. 1973
						45 F (LD_{50})	
7	Rat (Sprague-Dawley)	once (GO)				25 M (25% died)	Seefeld et al. 1984
8	Rat (Sprague-Dawley)	once (GO)				43 (LD_{50})	Stahl et al. 1992

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
9	Rat (Fischer- 344)	once (GO)				164 M (LD_{50})	Walden and Schiller 1985
10	Mouse (C57BL/6)	once (GO)				360 M (69% died)	Kelling et al. 1985
11	Mouse (C57BL)	once (GO)				146 M (LD_{50})	Smith et al. 1981
12	Mouse (C57BL/6N)	once (GO)				100 M (LD_{50})	Weber et al. 1995
13	Mouse (DBA/2)	once (GO)				>3000 M (LD_{50})	Weber et al. 1995
14	Gn pig (Hartley)	11 d (F)				0.03 (10% died)	Decaprio et al. 1986
15	Gn pig (Hartley)	once (GO)				1.75 M (LD_{50})	McConnell et al. 1984
16	Gn pig (Hartley)	once (GO)				0.6 M (LD_{50}) 2.1 F (LD_{50})	Schwetz et al. 1973
17	Hamster (Syrian)	once (GO)				5051 M (LD_{50})	Henck et al. 1981
18	Hamster (Golden Syrian)	once (GO)				1157 (LD_{50})	Olson et al. 1980a

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
19	Dog (Beagle)	once (C)				3000 M (2/2 died)	Schwetz et al. 1973
20	Rabbit (New Zealand)	Gd 6-15 1 x/d (GO)				1 F (4/10 dams died)	Giavini et al. 1982
21	Rabbit (New Zealand)	once (GO)				115 (LD_{50})	Schwetz et al. 1973
22	Mink	once (GO)				4.2 M (LD_{50})	Hochstein et al. 1988
	Systemic						
23	Monkey (Rhesus)	once (GO)	Cardio		70 F (reduced heart weight)		McConnell et al. 1978
			Gastro		70 F (epithelial hyperplasia of the stomach)		
			Hemato		70 F (mild anemia)		
			Hepatic		70 F (increased liver weight)		
			Renal		70 F (epithelial hyperplasia in the renal pelvis)		
			Dermal		70 F (blepharitis, acne, facial alopecia)		
			Bd Wt			70 F (28% weight loss)	

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
24	Rat (Sprague-Dawley)	once (GO)	Endocr		25 (decreased corticosterone levels on days 14 and 21 after dosing)		Balk and Piper 1984
25	Rat (Sprague-Dawley)	once (GO)	Gastro		100 M (malabsorption of glucose)		Ball and Chabra 1981
			Bd Wt	5 M		100 M (25% decrease weight)	
26	Rat (Sprague-Dawley)	once (GO)	Endocr		50 M (increased serum ACTH; increased serum corticosterone on days 1 and 5 but decrease on days 10 and 14)		Bestervelt et al. 1993
27	Rat (Sprague-Dawley)	once (GO)	Cardio	75 M			Christian et al. 1986a
			Gastro	75 M			
			Hepatic		25 M (enlarged hepatocytes)		
			Renal		25 M (dilated convoluted tubules)		
			Bd Wt			25 M (36-48% body weight loss)	

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
28	Rat (Wistar)	1 x/d 10 d (GO)	Bd Wt	25 M	50 M (significant but unspecified reduction in body weight gain)		De Heer et al. 1994a
29	Rat (Wistar)	once (GO)	Bd Wt	25 M			De Heer et al. 1994b
30	Rat (Long- Evans)	once (GO)	Endocr	5.3 F	12 F (44% decrease in serum total T4 four days after dosing)		Fan and Rozman 1995
31	Rat (CRCD)	2 wk 7 d/wk 1 x/d (GO)	Bd Wt	0.125		0.5 (28% reduced weight gain in dams)	Giavini et al. 1983
32	Rat (Sprague-Dawley)	once (GO)	Hepatic		6.25 (altered vitamin A storage)		Hakansson et al. 1989c
33	Rat (Sprague-Dawley)	once (GO)	Hepatic		100 (ED_{50} for liver enlargement)		Hanberg et al. 1989
			Bd Wt		89 (ED_{50} for reduced body weight gain)		

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL				Reference
					Less Serious (ug/kg/day)		Serious (ug/kg/day)		
34	Rat (Sprague-Dawley)	3 d 1 x/d (GO)	Cardio				40 F	(27% decrease heart rate, 20% decrease mean blood pressure)	Hermansky et al. 1988
			Hepatic				40 F	(hepatocyte enlargement, focal sinusoidal dilation, pericentral acinar necrosis, nuclear vacuolation, portal inflammation)	
			Endocr		40 F	(decreased thyroxine levels)			
35	Rat (Fischer- 344)	once (GO)	Hepatic		100 M	(degenerative changes)			Kelling et al 1985
			Bd Wt				100 M	(40% weight loss)	
36	Rat (Sprague-Dawley)	once (GO)	Cardio		6.25 M	(increased basal tension of the left atria)			Kelling et al. 1987
37	Rat (Sprague-Dawley)	once (GO)	Endocr		50 M	(decreased adrenal 21-hydroxylase activity)			Mebus and Piper 1986
38	Rat (Sprague-Dawley)	once (GO)	Bd Wt		6.25 M	(10% weight loss)	100 M	(23% weight loss)	Moore et al. 1985

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
39	Rat (Sprague-Dawley)	once (GO)	Renal	5 M			Pegg et al. 1976
40	Rat (Sprague-Dawley)	once (GO)	Endocr	0.032 M	0.32 M (decreased serum T4 and T3 levels)		Roth et al. 1988
			Bd Wt	3.2 M		10.6 M (30% decrease body weight gain)	
41	Rat (Sprague-Dawley)	once (GO)	Bd Wt			15 M (100% decreased body weight gain)	Seefeld and Peterson 1984
42	Rat (Sprague-Dawley)	once (GO)	Bd Wt		5 M (transiently decreased body weight gain)	50 M (50% body weight loss)	Seefeld et al. 1984a
43	Rat (Sprague-Dawley)	once (GO)	Bd Wt			15 M (60% decreased weight gain)	Seefeld et al. 1984b
44	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)	Bd Wt	0.125 F	0.5 F (decreased body weight gain in dams)		Sparschu et al. 1971
45	Rat (Sprague-Dawley)	once (GO)	Gastro		19 M (increased weight of antral mucosa)		Theobald et al. 1991

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
46	Rat (Fischer- 344)	once (GO)	Hepatic		45 M (hyperlipidemia, hypoglycemia)		Walden and Schiller 1985
			Bd Wt			164 M (38.9% body weight loss at lethal dose)	
47	Rat (CD)	10-14 d 1 x/d (GO)	Hemato		10 (increase in packed cell volume, erythrocytes, neutrophils; decrease in mean corpuscular hemoglobin and platelet count)		Weissberg and Zinkl 1973
48	Mouse (CD-1)	10 d Gd 7-16 1 x/d	Hepatic		25 F (increased liver weight in dams)		Courtney 1976
			Bd Wt	50 F		100 F (22% decrease weight gain in dams)	
49	Mouse (CD-1)	14 d 1 x/d (GO)	Bd Wt	10 F			Courtney 1976
50	Mouse (B6C3F1)	once (GO)	Hepatic	1 F	10 F (23% increase in liver weight; significant induction of CYP1A1 and 1A2 activities)		Diliberto et al. 1995
			Bd Wt	10 F			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
51	Mouse (A2G-hr/+)	once (GO)	Hepatic			75 (3-fold increase in serum ALT, 100-fold increase in hepatic porphyrins, paracentral necrotic foci, fatty changes in midzonal region)	Greig 1984, 1987
			Dermal		75 (skin thickening)		
52	Mouse (C57BL/6)	once (GO)	Hepatic		1000 (ED_{50} for liver enlargement)		Hanberg et al. 1989
			Bd Wt		890 (ED_{50} for reduced body weight gain)		
53	Mouse (B6C3F1)	14 d 1 x/d (GO)	Resp	1 F			Holsapple et al. 1986
			Hemato	1 F			
			Hepatic		1 F (hydropic degeneration, increased liver weight induced microsomal enzymes)		
			Renal	1 F			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
54	Mouse (C57BL/6N)	once (G)	Hepatic	0.5 M	15 M (35% increase in relative liver weight in young mice; significant induction of hepatic EROD and ACOH activities)		Pegram et al. 1995
			Bd Wt	15 M			
55	Mouse (C57BL/6J)	10 d Gd 6-15 1 x/d (GO)	Hepatic		0.5 F (38% increase in relative liver weight)		Silkworth et al. 1989b
			Bd Wt	8 F			
56	Mouse (CF-1)	10 d Gd 6-15 1 x/d (GO)	Hepatic	1.0 F	3.0 F (increased liver weight in dams)		Smith et al. 1976
			Bd Wt	3.0 F			
57	Mouse (C57BL/10)	once (GO)	Hepatic	15		50 (50-fold increase in hepatic porphyrins)	Smith et al. 1981

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
58	Mouse (C57BL/6N)	once (GO)	Hepatic	1 M	3 M (increased relative liver weight and EROD activity; decreased PEPCK activity)		Weber et al. 1995
			Renal	235 M			
			Endocr	0.03 M	0.1 M (significant decrease in serum T3 and T4)		
			Bd Wt	235 M			
59	Mouse (DBA/2)	once (GO)	Hepatic	10 M	97.5 M (increased liver weight and EROD activity; decreased PEPCK activity)		Weber et al. 1995
			Renal	1500 M	1950 M (decreased kidney weight)		
			Endocr	10 M	97.5 M (significant decrease in serum T3 and T4)		
			Bd Wt	375 M	1500 M (17% decrease in weight gain)		
60	Mouse (CD-1)	once (GO)	Hemato		1 F (reversible decreases in leuko- and lymphocyte counts)		Zinkl et al. 1973

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
61	Gn pig (Hartley)	once (GO)	Bd Wt		1.8 (ED_{60} for reduced body weight gain)		Hanberg et al. 1989
62	Gn pig (Hartley)	once (G)	Hepatic		0.1 (focal necrosis)		Turner and Collins 1983
63	Hamster (Golden Syrian)	once (GO)	Hepatic		14 (ED_{50} for liver enlargement)		Hanberg et al. 1989
			Bd Wt		1000 (ED_{60} for reduced body weight gain)		
64	Hamster (Syrian)	once (GO)	Gastro	6000 M			Henck et al. 1981
			Dermal	600 M	1000 M (rough hair)		
			Bd Wt	600 M	1000 M (decreased body weight gain)		
65	Rabbit (New Zealand)	Gd 6-15 1 x/d (GO)	Bd Wt	0.1 F		0.25 F (44% decreased weight gain in dams)	Giavini et al. 1982

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
66	mink	once (GO)	Cardio	2.5 M	5 M (increased heart relative weight)		Hochstein et al. 1988
			Gastro	2.5 M		5 M (gastrointestinal ulcerations)	
			Hemato	7.5 M			
			Hepatic	2.5 M	5 M (pale liver)		
			Renal	2.5 M	5 M (increased kidney relative weight)		
			Endocr		2.5 M (increased adrenal absolute weight)		
			Bd Wt		2.5 M (11% weight loss)	5 M (27% weight loss)	
	Immunological/Lymphoreticular						
67	Monkey (Rhesus)	once (GO)				70 F (severe atrophy of the thymus)	McConnell et al 1978a
68	Rat (Sprague-Dawley)	once (GO)			25 M (reduced germinal centers and increased hemosiderin deposits in the spleen)		Christian et al. 1986a
69	Rat (Wistar)	1 x/d 10 d (GO)		1 M	5 M (reduced relative thymus weight)		De Heer et al. 1994a

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
70	Rat (Wistar)	once (GO)			25 M (reversible thymic atrophy starting on day 13)		De Heer et al. 1994b
71	Rat (Wistar)	1 x/d 4 d (GO)			1 M (reduced number of immature CD4CD8 double positive thymocytes; decreased thymus weight)		De Heer et al. 1994b
72	Rat (Wistar)	once (GO)			50 M (decreased absolute thymus weight)		DeWall et al. 1992
73	Rat (Sprague-Dawley)	once (GO)			10 M (altered cell-mediated immunity judged by an increased delayed-type hypersensitivity reaction)		Fan et al. 1996
74	Rat (Sprague-Dawley)	once (GO)				26 (ED_{50} for thymic atrophy)	Hanberg et al. 1989
75	Rat (Fischer- 344)	1 x/d 14 d (GO)			0.72 F (supression in virus-augmented NK cell activity)		Yang et al. 1994

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
76	Mouse (B6C3F1)	once (GO)			5 (reduced polymorphonuclear activity)		Ackermann et al. 1989
77	Mouse (C57BL/6)	9 d Gd 6-14 1 x/d (GO)				1.5 F (inhibition of thymocyte maturation fetal thymocytes)	Blaylock et al. 1992
78	Mouse (B6C3F1)	once (GO)		0.005[b] F	0.01 F (decreased influenza virus host resistance)		Burleson et al. 1996
79	Mouse (C57BL/6N)	once (GO)		2.5 M	5 M (decreased cytotoxic T lymphocyte activity)		De Krey and Kerkvliet 1995
80	Mouse (B6C3F1)	once (GO)		1 F	10 F (28% decrease in thymus weight 14 days after dosing)		Diliberto et al. 1995
81	Mouse (C57BL/6)	once (GO)				280 (ED_{50} for thymic atrophy)	Hanberg et al. 1989
82	Mouse (B6C3F1)	once (GO)		0.5 F	1.0 F (suppressed antibody response)		Holsapple et al. 1986
83	Mouse (B6C3F1)	once (GO)			20 F (18% reduction in serum Complement 3)		Lin and White 1993

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
84	Mouse (C57BL/6J)	10 d Gd 6-15 1 x/d (GO)		0.5 F	1 F (decreased relative thymus weight)		Silkworth et al. 1989b
85	Mouse (B6C3F1)	once (GO)			14 F (suppressed serum complement activity)		White et al. 1986
86	Mouse (B6C3F1)	14 d 1 x/d (GO)			0.01 F (suppressed serum complement activity)		White et al. 1986
87	Gn pig (Hartley)	once (GO)				0.8 (ED_{50} for thymic atrophy)	Hanberg et al. 1989
88	Gn pig (NS)	once (GO)				6 (thymic atrophy)	Umbreit et al. 1985
89	Hamster (Golden Syrian)	once (GO)				48 (ED_{50} for thymic atrophy)	Hanberg et al. 1989
	Neurological						
90	Rat (CRCD)	2 wk 7 d/wk 1 x/d (GO)		0.5	2 (decreased activity in dams)		Giavini et al. 1983
91	Rat (Sprague-Dawley)	once (GO)			5 M (decreased motor activity)		Seefeld et al. 1984a

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
92	Mink	once (GO)		2.5 M	5 M (increased brain relative weight)		Hochstein et al. 1988
	Reproductive						
93	Monkey (Rhesus)	once (GO)				1.0 (abortions in 10/12)	McNulty 1984
94	Rat (Sprague-Dawley)	once (GO)				10 M (ED_{50} altered regulation of leutinizing hormone secretion)	Bookstaff et al. 1990a
95	Rat (CRCD)	2 wk 7 d/wk 1 x/d (GO)		0.125		0.5 F (increased pre- and post-implantation loss)	Giavini et al. 1983
96	Rat (Wistar)	7 d 1x/d (GO)			4 (epididymal inflammation)		Khera and Ruddick 1973
97	Rat (Sprague-Dawley)	once 1 x/d (GO)		3 F		10 F (increased luteinizing and follicle stimulating hormone levels, altered ovulation)	Li et al. 1995a
98	Rat (Sprague-Dawley)	once 1 x/d (GO)				10 F (irregular estrous cycle and ovulation)	Li et al. 1995b

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
99	Rat (Sprague-Dawley)	once (GO)			4.5 M (decreased seminal vesicle weight)		Moore et al. 1985
100	Rat (Sprague-Dawley)	once (GO)				12.5 M (decreased plasma testosterone levels)	Moore et al. 1985
101	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		0.03 F		0.125 F (increased resorptions)	Sparschu et al. 1971
102	Mouse (CF-1)	10 d Gd 6-15 1 x/d (GO)		0.1 F		1.0 F (increased resorptions)	Smith et al. 1976
103	Rabbit (New Zealand)	10 d Gd 6-15 1 x/d (GO)		0.1		0.25 (increased post- implantation loss)	Giavini et al. 1982
	Developmental						
104	Monkey (Rhesus)	Gd 40 1 x/d (GO)				1 (2/3 fetuses died)	McNulty 1984
105	Rat (Holtzman)	Gd 15 1 x/d (GO)				1.0 M (demascularization and feminization of sexual behavior; delayed puberty)	Bjerke and Peterson 1994

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
106	Rat (Holtzman)	Gd 15 1 x/d (GO)				0.7 M (impaired development of reproductive system)	Bjerke et al. 1994a
107	Rat (Holtzman)	Gd 15 1 x/d (GO)				0.7 M (demascularization and feminization of sexual behavior)	Bjerke et al. 1994b
108	Rat (Sprague-Dawley)	25, 27, 29, and 31 days of age 1 x/d (GO)			2.5 F (decreased mammary gland size)		Brown and Lamartiniere 1995
109	Rat (Sprague-Dawley)	once Gd 15 (GO)				1 F (alteration in mammary gland differentiation in 50-day old pups; increased number of chemically-induced mammary adenocarcinomas in pups)	Brown et al. 1998
110	Rat (Holtzman)	once (GO)			1 F (decreased serum estrogen levels in female offspring)		Chaffin et al. 1996
111	Rat (Holtzman)	once (GO)		1 F			Chaffin et al. 1997

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL				Reference
					Less Serious (ug/kg/day)		Serious (ug/kg/day)		
112	Rat (F344)	Ld 0, 7, 14 1 x/d (GO)					5	(reversible suppression of cell-mediated immunity in offspring)	Faith and Moore 1977
113	Rat (Fischer- 344)	once (GO)			1	(alterations in lymphocyte phenotypes)			Gehrs et al. 1979a
114	Rat (Fischer- 344)	once (GO)			3	(alterations in lymphocyte phenotypes)			Gehrs et al. 1979b
115	Rat (Fischer- 344)	once (GO)			1	(alterations in lymphocyte phenotypes and decreased DTH response)			Gehrs et al. 1979b
116	Rat (CRCD)	2 wk 7 d/wk 1 x/d (GO)		0.5			2	(reduced number of live fetuses, fetal malformation)	Giavini et al. 1983
117	Rat (Long- Evans)	Gd 15 1 x/d (GO)			1 M	(decreased core body temperature)			Gordon et al. 1995

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
118	Rat (Long- Evans)	Gd 8 1 x/d (GO)				1 F (malformations of external genitalia, decreased fertility, shortened reproductive lifespan)	Gray and Ostby 1995
119	Rat (Long- Evans)	Gd 15 1 x/d (GO)				1 F (malformations of external genitalia, decreased fertility)	Gray and Ostby 1995
120	Rat (Holtzman)	Gd 15 1 x/d (GO)				1 F (malformations of external genitalia, decreased fertility)	Gray and Ostby 1995
121	Rat (Long- Evans)	Gd 8 or 15 1 x/d (GO)				1 M (impaired development of reproductive system)	Gray et al. 1995
122	Rat (Long- Evans)	once (GO)		0.05 F	0.20 F (urogenital morphological alterations, presence of vaginal thread, and cleft phallus)		Gray et al. 1997a

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL				Reference
					Less Serious (ug/kg/day)		Serious (ug/kg/day)		
123	Rat (Long- Evans)	once (GO)			1 F	(urogenital morphological alterations, presence of vaginal thread, and cleft phallus)			Gray et al. 1997a
124	Rat (Long- Evans)	once (GO)			0.05 M	(reduction in ejaculated sperm count)			Gray et al. 1997a
125	Rat (Sprague-Dawley)	Ld 1 (GO)					10	(thymic atrophy, liver enlargement, and decreased weight gain in pups)	Hakansson et al. 1987
126	Rat (Holtzman)	once (GO)			1 F	(decreased number of antral and preantral ovarian follicles)			Heimler et al. 1998
127	Rat (Long- Evans)	Gd 8 1 x/d (GO)		1			5	(cleft palate, thymic atrophy, decreased number of live fetuses)	Huuskonen et al. 1994

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
128	Rat (Han/Wistar)	Gd 8 1 x/d (GO)		1		10 (hydronephrosis, thymic atrophy, gastrointestinal hemorrhage, decreased number of live fetuses)	Huuskonen et al. 1994
129	Rat (Han/Wistar)	Gd 12 1 x/d (GO)		1		10 (hydronephrosis, gastrointestinal hemorrhages, decreased number of live fetuses)	Huuskonen et al. 1994
130	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		0.125		0.25 (subcutaneous edema, hemorrhages in GI tract and brain)	Khera and Ruddick 1973
131	Rat (Holtzman)	Gd 15 (GO)			0.064 (decreased testosterone)	0.16 M (delayed testis descent) 0.40 M (decreased growth during lactation--male pups)	Mably et al. 1992a
132	Rat	Gd 15 (GO)				0.064 (decreased masculine sexual behavior in male offspring)	Mably et al. 1992b
133	Rat	Gd 15 (GO)				0.064 M (reduced sperm production in offspring at all ages)	Mably et al. 1992c

[a]

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
134	Rat (Sprague-Dawley)	Gd10 (GW)				1.5 (fetal mortality, thymic dysfunction)	Olson and McGarrigle 1992
						3.6 (cleft palate)	
135	Rat (Sprague-Dawley)	Gd 10-16 1x/d (GO)		0.025 F	0.1 F (decreased thyroxine levels)		Seo et al. 1995
136	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		0.03		0.125 (intestinal hemorrhage in fetuses)	Sparschu et al. 1971
137	Mouse (C57BL/6N)	Gd 10 or 12 1 x/d (GO)				6 (cleft palates)	Abbott and Birnbaum 1989
138	Mouse (C57BL/6N)	Gd 10 (GO)				12 (fetal hydronephrosis, hydroureter)	Abbott et al. 1987a
139	Mouse (C57BL/6N)	Gd 10-13 1 x/d (GO)		3			Abbott et al. 1992
140	Mouse (C57B1/6)	Gd 6-14 1 x/d (GO)				.1.5 M (thymic atrophy and delayed thymocyte maturation)	Blaylock et al. 1992

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
141	Mouse (C57BL/6J)	Gd 9 1 x/d (GO)				15 (cleft palate)	Dasenbrock et al. 1992
142	Mouse (DBA2J)	Gd 9 1 x/d (GO)				150 (cleft palate)	Dasenbrock et al. 1992
143	Mouse (B6C3F1)	9 d Gd 6-14 (GO)				1.5 (immunosupression in pups, thymic atrophy, abnormal fetal thymoctye-maturation)	Holladay et al. 1991
144	Mouse (B6C3F1)	Gd 14 Ld 1, 7, 14 1 x/d (GO)			1 (increased neutrophils in pups)	5 (bone marrow toxicity)	Luster et al. 1980
145	Mouse (C57B1/6)	Gd 10 1 x/d (GO)				1 (hydronephrosis)	Moore et al. 1973
146	Mouse (NMR1)	4 d Gd 14-17 1 x/d (GO)				12.5 (75% pup mortality)	Nau et al. 1986
147	Mouse (NMRI)	10 d Gd 6-15 1 x/d (GO)		0.3		3.0 (cleft palates)	Neubert and Dillmann 1972

[a]

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)		Reference
148	Mouse (C57BL/6J, DBA/2J)	10 d Gd 6-15 1 x/d (GO)				0.5	(hydronephrosis)	Silkworth et al. 1989b
149	Mouse (CF-1)	10 d Gd 6-15 1 x/d (GO)		0.1		1.0	(cleft palate)	Smith et al. 1976
150	Gn pig (Hartley)	Gd 14 (GO)		0.15		1.5	(fetal mortality, increase resorption, decreased spleen and thymus weight)	Olson and McGarrigle 1992
151	Hamster (Golden Syrian)	Gd 11 1 x/d (GO)				2 M	(impaired development of reproductive system)	Gray et al. 1995
						2 M	(nephrosis)	
152	Hamster (Golden Syrian)	Gd 7 or 9 (GO)				1.5	(hydronephrosis, thymic dysfunction)	Olson and McGarrigle 1992
						18	(fetal mortality)	
153	Rabbit (New Zealand)	10 d Gd 6-15 1 x/d (GO)				0.1	(skeletal anomalies hydronephrosis)	Giavini et al. 1982

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
INTERMEDIATE EXPOSURE							
	Death						
154	Monkey (Rhesus)	9 mo 7 d/wk (F)				0.011 F (5/8 died)	Allen et al. 1977
155	Monkey (Rhesus)	2-33 mo 7 d/wk (F)				0.02 (5/8 died by 2 months)	Hong et al. 1989
156	Monkey (Rhesus)	3 wk 3 d/wk 1 x/d (GO)				0.6 (2/2 died)	McNulty 1984
157	Rat (Sprague-Dawley)	10 wk 1 x/ wk (GO)				1.6 M (4/7 deaths; mean time to death was 54 days)	Li and Rozman 1995
158	Rat (Sprague-Dawley)	48 wk 7 d/wk (F)				3.4 M (100% mortality by 3rd week)	Van Miller et al. 1977
159	Mouse (C57B/6)	25 wk 3 d/wk 1 x/d (GO)				3 F (70% died)	Umbreit et al. 1987
160	Gn pig (Hartley)	35 d 7 d/wk (F)				0.8 (LD_{50} for 27 days)	DeCaprio et al. 1986

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
	Systemic						
161	Monkey (Rhesus)	9 mo 7 d/wk (F)	Resp			0.011 F (lung hemorrhage)	Allen et al. 1977
			Cardio			0.011 F (hemorrhage in epicardium, myocardium, and endocardium)	
			Gastro			0.011 F (gastric ulcers)	
			Hemato			0.011 F (pancytopenia, bone marrow atrophy)	
			Musc/skel			0.011 F (hemorrhage in muscles from the extremities)	
			Hepatic		0.011 F (epithelial biliary hyperplasia)		
			Renal		0.011 F (tubular epithelial hyperplasia)		
			Dermal			0.011 F (periorbital edema, facial alopecia, squamous metaplasia, hyperkeratoses; subcutaneous edema)	
			Bd Wt		0.011 F (12% weight loss)		

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
162	Monkey (Rhesus)	3 wk 3 d/wk 1 x/d (GO)	Resp	0.02 F	0.1 F (epistaxis)		McNulty 1984
			Gastro	0.02 F	0.1 F (metaplasia of gastric mucosa)		
			Hemato	0.02 F		0.1 F (anemia, bone marrow hypoplasia)	
			Hepatic		0.1 F (biliary hyperplasia)		
			Dermal	0.02 F		0.1 F (hair loss, periorbital edema, hyperkeratosis, squamous metaplasia of sebaceaus glands)	
			Bd Wt	0.02 F		0.1 F (weight loss)	
163	Rat (Sprague-Dawley)	16 wk 1 x/wk (GO)	Hepatic	0.01 F	0.14 F (hepatic porphyria)		Goldstein et al. 1982
			Bd Wt	0.01 F	0.14 F (16% reduction in body weight gain)		
164	Rat (Sprague-Dawley)	10 wk 1 x/ wk (GO)	Endocr	0.003 M	0.03 M (almost 50% reduction in total serum T4)		Li and Rozman 1995
			Bd Wt	0.03 M		0.2 M (38% decrease in body weight gain)	

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
165	Rat (Osborne-Mendel)	13 wk 2 d/wk 1 x/d (GO)	Hepatic		0.07 F (unspecified lesions in female)		NTP 1982b
			Bd Wt		0.07 (unspecified decrease in weight gain)		
166	Rat (Sprague-Dawley)	30 wk 1 x/2 wk (GO)	Endocr	0.011 F	0.036 F (reduction in serum T4)		Sewall et al. 1995
167	Rat (Sprague-Dawley)	13 wk (F)	Hepatic		0.014 F (reduction in hepatic retinol)		Van Birgelen et al. 1995
			Renal	0.026 F	0.047 F (increased relative kidney weight)		
			Endocr	0.026 F	0.047 F (reduction in total serum T4)		
			Bd Wt	0.026 F	0.047 F (10% reduction in body weight gain)	1.02 F (72% reduction in body weight gain)	

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
168	Rat (Sprague-Dawley)	13 wk 1 x/2 wk (GO)	Hemato			0.8 M (decrease in platelet count; increase in prothrombin time in some rats)	Viluksela et al. 1994
			Hepatic		0.8 M (increased relative liver weight and liver EROD activity; decreased liver PEPCK activity)		
			Endocr		0.8 M (decrease in total serum T4)		
			Bd Wt			0.8 M (30% decrease in body weight gain)	
169	Rat (CD)	6 wk 1 d/wk 1 x/d (GO)	Hemato	0.71 F			Vos et al. 1973
			Bd Wt	0.14 F	0.71 F (14% decreased body weight gain)		
170	Rat (CD)	30 d 1 x/d (GO)	Hemato		0.1 F (trombocytopenia)		Zinkl et al. 1973
			Hepatic	0.1 F	1 F (increased serum transaminase)		

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
171	Mouse (B6C3F1)	13 wk 5 d/wk (F)	Hepatic	0.150 F			DeVito et al. 1994
			Bd Wt	0.150 F			
172	Mouse (B6C3F1)	13 wk 2 d/wk 1 x/d (GO)	Hepatic	0.28 F	0.7 F (unspecified lesions in females)		NTP 1982b
173	Mouse (C57BL/6Jfh)	4 wk 1 d/wk 1 x/d (GO)	Hepatic	5 M	10 M (hepatocellular cytomegaly)		Thigpen et al. 1975
			Bd Wt	10 M		20 M (36% decreased weight gain)	
174	Mouse (Swiss-Webster)	10 wk 7 d/wk (F)	Dermal	0.65 F	1.3 F (alopecia, edema in dams)		Thomas and Hinsdill 1979
175	Mouse	4 wk 1 d/wk 1 x/d (GO)	Bd Wt	0.71 M	3.6 M (17% reduced weight gain)		Vos et al. 1973

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)		LOAEL Serious (ug/kg/day)		Reference
176	Gn pig (Hartley)	90 d 7 d/wk (F)	Hemato	0.005					DeCaprio et al. 1986
			Hepatic	.0007	0.005	(hepatocellular inclusions, hypertriglyceridemia)			
			Bd Wt	.0007	0.005	(15-20% reduced weight gain)			
177	Gn pig (Hartley)	8 wk 1 d/wk 1 x/d (GO)	Hemato		0.001 F	(decreased lymphocytes)			Vos et al. 1973
			Bd Wt	0.006	0.03 F	(14% decreased body weight gain)			
	Immunological/Lymphoreticular								
178	Monkey (Rhesus)	9 mo 7 d/wk (F)					0.011	(lymph nodes atrophy)	Allen et al. 1977
179	Rat (Sprague-Dawley)	90 d (F)		0.001	0.01	(decreased thymus weight in F3)			Murray et al 1979

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
180	Rat (Sprague-Dawley)	13 wk (F)			0.014 F (21% reduction in final thymus weight)	1.02 F (80% reduction in final thymus weight)	Van Birgelen et al. 1995
181	Rat (Sprague-Dawley)	13 wk 1 x/2 wk (GO)			0.8 M (significant reduction in absolute and relative thymus weight)		Viluksela et al. 1994
182	Rat (CD)	6 wk 1 d/wk 1 x/d (GO)		0.14 F	0.71 F (decreased thymus weight slight cortical atrophy)		Vos et al. 1973
183	Mouse (B6C3F1)	13 wk 5 d/wk (F)		0.150 F			DeVito et al. 1994
184	Mouse (C57BL/6Jfh)	4 wk 1 d/wk 1 x/d (GO)		0.5 M		1 M (increased mortality after infection)	Thigpen et al. 1975
185	Mouse (C57BL/6, DBA/2)	5-8 wk 1 d/wk 1 x/d (GO)				0.5 M (suppoessed humoral activity in C57BL/6 strain)	Vecchi et al. 1983a

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
186	Mouse	4 wk 1 d/wk 1 x/d (GO)		0.14 M		0.71 M (decreased cell-mediated immunity)	Vos et al. 1973
187	Gn pig (Hartley)	90 d 7 d/wk (F)		0.0007[c]	0.005 (37% decrease in absolute thymus weight; 24% decrease in relative thymus weight)	0.028 (atrophy of thymus cortex in 1/4 males and 2/4 females)	DeCaprio et al. 1986
188	Gn pig (Hartley)	8 wk 1 d/wk 1 x/d (GO)			0.001 F (decreased lymphocytes)	0.03 F (decreased humoral immunity, thymic atrophy)	Vos et al. 1973
	Reproductive						
189	Monkey (Rhesus)	3 wk 3 d/wk 1 x/d (GO)		0.02		0.1 (abortions in 3/4 monkeys)	McNulty 1984
190	Rat (Sprague-Dawley)	90 d (F)		0.001		0.01 (decreased fertility in F1 and F2)	Murray et al. 1979
191	Rat (Sprague-Dawley)	4 wk 7 d/wk (F)		0.286 M		3.4 M (reduced spermatogenesis)	Van Miller et al. 1977a

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
192	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		0.150 F			DeVito et al. 1994
193	Mouse (Swiss-Webster)	10 wk 7 d/wk (F)		0.65		1.3 (increased mortality in offspring)	Thomas and Hinsdill 1979
194	Mouse (C57B/6)	25 wk 3 d/wk 1 x/d (GO)				3 F (estrus blocked)	Umbreit et al. 1987
195	Mouse (C57B/6)	30 wk 1 d/wk 1 x/d (GO)		3 M			Umbreit et al. 1988
	Developmental						
196	Rat (Sprague-Dawley)	90 d (F)		0.001		0.01 (decreased neonatal survival and neonatal growth in F1 and F2)	Murray et al. 1979
197	Mouse (Swiss-Webster)	10 wk 7 d/wk (F)				0.35 (thymus atrophy)	Thomas and Hinsdill 1979
198	Mouse (C57B/6)	30 wk 1 d/wk 1 x/d (GO)		3			Umbreit et al. 1988

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)		LOAEL Serious (ug/kg/day)		Reference
	CHRONIC EXPOSURE								
	Death								
199	Rat (Sprague-Dawley)	2 yr 7 d/wk (F)					0.1	(increased mortality)	Kociba et al. 1978
200	Mouse (B6C3)	52 wk 1 d/wk 1 x/d (GO)					0.36	(increased mortality)	Della Porta et al. 1987
201	Mouse (Swiss)	1 yr 1 d/wk (GO)					1.0 M	(decreased survival)	Toth et al. 1979
	Systemic								
202	Rat (Sprague-Dawley)	2 yr 7 d/wk (F)	Resp	0.01	0.1	(focal alveolar hyperplasia)			Kociba et al. 1978a
			Cardio	0.01			0.1	(myocardial degeneration, periarteritis)	
			Gastro	0.1					
			Hemato	0.01	0.1	(decreased erythocytes)			
			Musc/skel	0.1					
			Hepatic		0.001 F	(hepatocellular alterations in females)	0.01	(severe and extensive hepatic necrosis)	
			Renal	0.1					
			Bd Wt		0.1	(unspecified decrease in body weight gain)			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
203	Rat (Osborne-Mendel)	104 wk 2 d/wk (GO)	Resp	0.071			NTP 1982b
			Cardio	0.071			
			Gastro	0.071			
			Hemato	0.071			
			Musc/skel	0.071			
			Hepatic	0.0071		0.071 (toxic hepatitis)	
			Renal	0.071			
			Endocr	0.071			
			Dermal	0.071			
			Ocular	0.071			
			Bd Wt			0.0014 (21% decrease in body weight gain)	
204	Rat (Sprague-Dawley)	78 wk 7 d/wk (F)	Gastro	0.286			Van Miller et al. 1977
			Hemato	0.286			
			Hepatic	0.286			
			Bd Wt	0.057		0.286 M (26% decreased weight gain)	

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)		LOAEL Serious (ug/kg/day)		Reference
205	Mouse (B6C3)	52 wk 1 x/wk (GO)	Dermal		0.36	(dermatitis)			Della Porta et al. 1987
			Bd Wt				0.36	(33% decreased weight gain)	
206	Mouse (B6C3F1)	104 wk 2 d/wk (GO)	Resp	0.3					NTP 1982b
			Cardio	0.3					
			Gastro	0.3					
			Hemato	0.3					
			Musc/skel	0.3					
			Hepatic	0.0071			0.071	(toxic hepatitis)	
			Renal	0.0071	0.071	(lymphocytic inflamatory infiltration in kidneys)			
			Endocr	0.3					
			Dermal	0.3					
			Ocular	0.3					
			Bd Wt	0.3					
207	Mouse (C57BL/6N)	14.5 mo 1 x/wk (GO)	Hemato	0.03 F					Oughton et al. 1995
			Bd Wt	0.03 F					

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
208	Mouse (Swiss)	1 yr 1 d/wk (GO)	Dermal		0.001 M (skin lesions and generalized amyloidosis in 5/44 mice; 0/38 in controls)		Toth et al. 1979
	Immunological/Lymphoreticular						
209	Monkey (Rhesus)	2-33 mo 7 d/wk (F)				0.002 (bone marrow and lymphoid tissue degeneration)	Hong et al. 1989
210	Monkey (Rhesus)	4 yr 12 mo/yr 7 d/wk (F)		0.001			Hong et al. 1989
211	Rat (Sprague-Dawley)	2 yr 7 d/wk (F)		0.01		0.1 (thymic atrophy)	Kociba et al. 1978
212	Rat (Osborne-Mendel)	104 wk 2 d/wk (GO)		0.071			NTP 1982b
213	Rat (Sprague-Dawley)	78 wk 7 d/wk (F)		0.286 M			Van Miller et al. 1977
214	Mouse (B6C3F1)	104 wk 2 d/wk (GO)		0.3			NTP 1982b

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference
215	Mouse (C57BL/6N)	14.5 mo 1 x/wk (GO)			0.03 F (decrease in the effector and memory T cell phenotypes)		Oughton et al. 1995
	Neurological						
216	Rat (Sprague-Dawley)	2 yr 7 d/wk (F)		0.01		0.1 (hemorrhage in brain)	Kociba et al. 1978
217	Rat (Osborne-Mendel)	104 wk 2 d/wk (GO)		0.071			NTP 1982b
218	Mouse (B6C3F1)	104 wk 2 d/wk (GO)		0.3			NTP 1982b
	Reproductive						
219	Monkey (Rhesus)	4 yr 12 mo/yr 7 d/wk (F)		0.00012 F		0.00064 F (50% increased abortions)	Bowman et al. 1989b; Hong et al. 1989
220	Monkey (Rhesus)	3.5-4 yr (F)		0.00012 F		0.00064 F (reduced reproduction)	Bowman et al. 1989b; Hong et al. 1989
221	Monkey (Rhesus)	3.5-4 years daily (F)			0.00012 F (moderate endometriosis)	0.00064 F (severe endometriosis)	Rier et al. 1993

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)		LOAEL Serious (ug/kg/day)		Reference
222	Rat (Sprague-Dawley)	2 yr 7 d/wk (F)		0.1					Kociba et al. 1978
223	Rat (Osborne-Mendel)	104 wk 2 d/wk (GO)		0.071					NTP 1982b
224	Mouse (B6C3F1)	104 wk 2 d/wk (GO)		0.3					NTP 1982b
	Developmental								
225	Monkey (Rhesus)	4 yr 7 d/wk (F)		.00012			0.00064	(decreased off-spring survival)	Bowman et al. 1989b
226	Monkey (Rhesus)	16 mo 7 d/wk (F)			0.00012[d]	(altered social behavior)			Schantz et al. 1992
227	Monkey (Rhesus)	3.5-4 yrs (F)					0.00064	(learning impairment)	Schantz et al. 1992; Bowman et al. 1989a
	Cancer								
228	Rat (Sprague-Dawley)	2 yr 7 d/wk (F)					0.1	(CEL: hepatocellular carcinoma, squamous cell carcinoma in lung and hard palate)	Kociba et al. 1978

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL			Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)		
229	Rat (Osborne-Mendel)	104 wk 2 d/wk (GO)				0.0071 M	(CEL: increased incidence of thyroid follicular cell adenoma or carcinoma)	NTP 1982b
						0.071 F	(CEL: increased incidence of neoplastic nodule in liver or hepatocellular carcinoma)	
230	Mouse (B6C3)	52 wk 1 x/wk (GO)				0.36	(CEL: hepatocellular adenoma or carcinoma)	Della Porta et al. 1987
231	Mouse (B6C3F1)	104 wk 2 d/wk (GO)				0.071 M	(CEL: increased incidence of hepatocellular adenoma or carcinoma)	NTP 1982b
						0.3 F	(CEL: increased inceidence of thyroid follicular cell adenoma and histiocytic lymphomas)	

Table 2-2. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL			Reference
					Less Serious (ug/kg/day)	Serious (ug/kg/day)		
232	Mouse (Swiss)	1 yr 1 d/wk (GO)				0.1	(CEL: hepatocellular carcinoma)	Toth et al. 1979

[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an acute-duration oral minimal risk level (MRL) of $2x10^{-4}$ µg/kg/day; dose divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) and by a modifying factor of 0.7 to adjust for the difference in higher bioavailability of 2,3,7,8-TCDD from oil gavage vehicle than from food.

[c] Used to derive an intermediate-duration oral MRL of $2x10^{-5}$ µg/kg/day; dose divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

[d] Used to derive a chronic-duration oral MRLof $1x10^{-6}$ µg/kg/day; dose divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

ACOH = acetanilide-4-hydroxylase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); ED_{50} = dose eliciting a 50% decrease or increase relative to controls; Endocr = endocrine; EROD = ethoxyresorufin-O-deethylase; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; LH = luteinizing hormone; M = male; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; PEPCK = phosphoenolpyruvate carboxykinase; RBC = red blood cell; Resp = respiratory; WBC = white blood cell; wk = week(s); yr = year(s): x = times.

Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral

Acute (≤14 days)

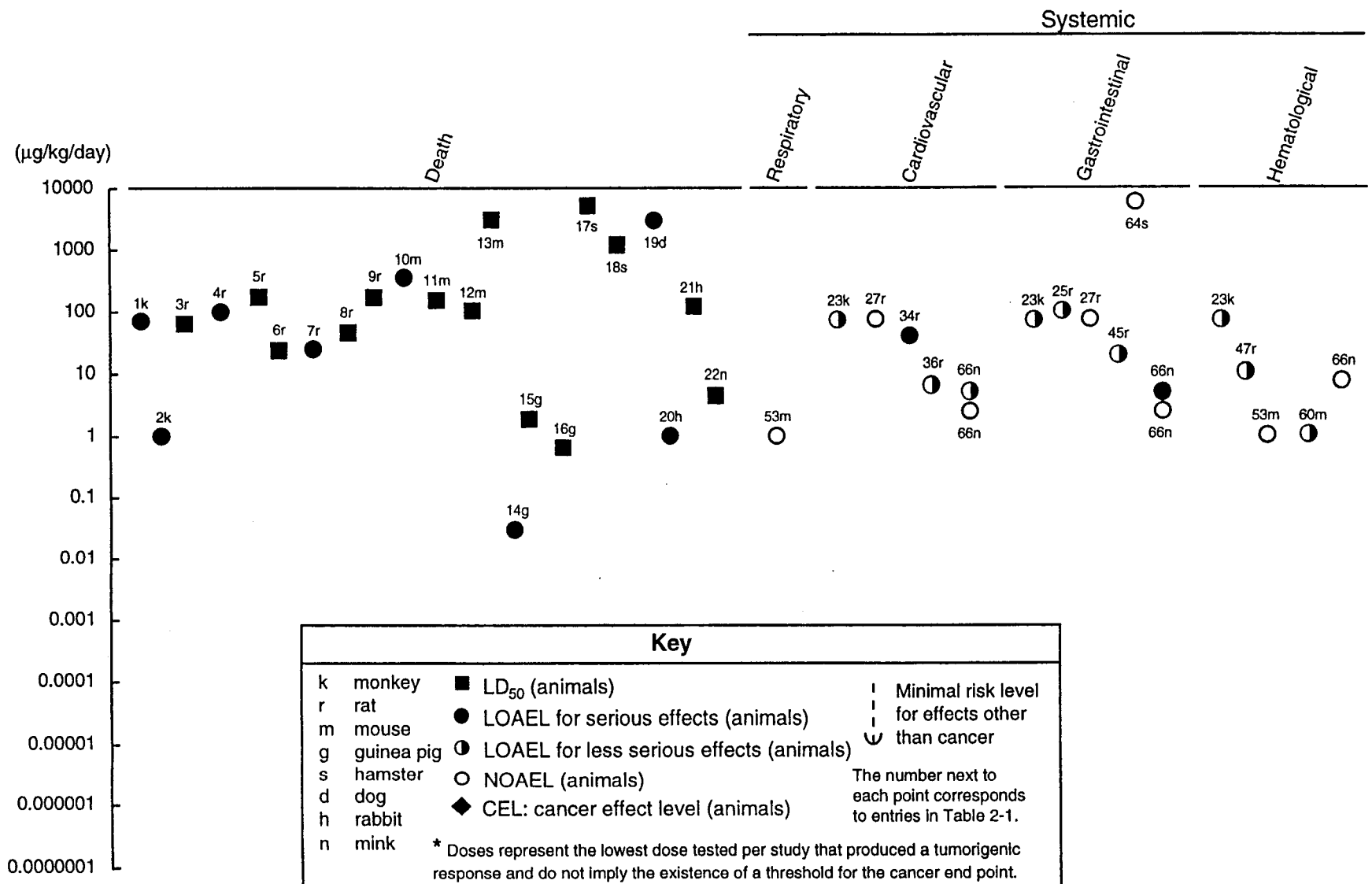
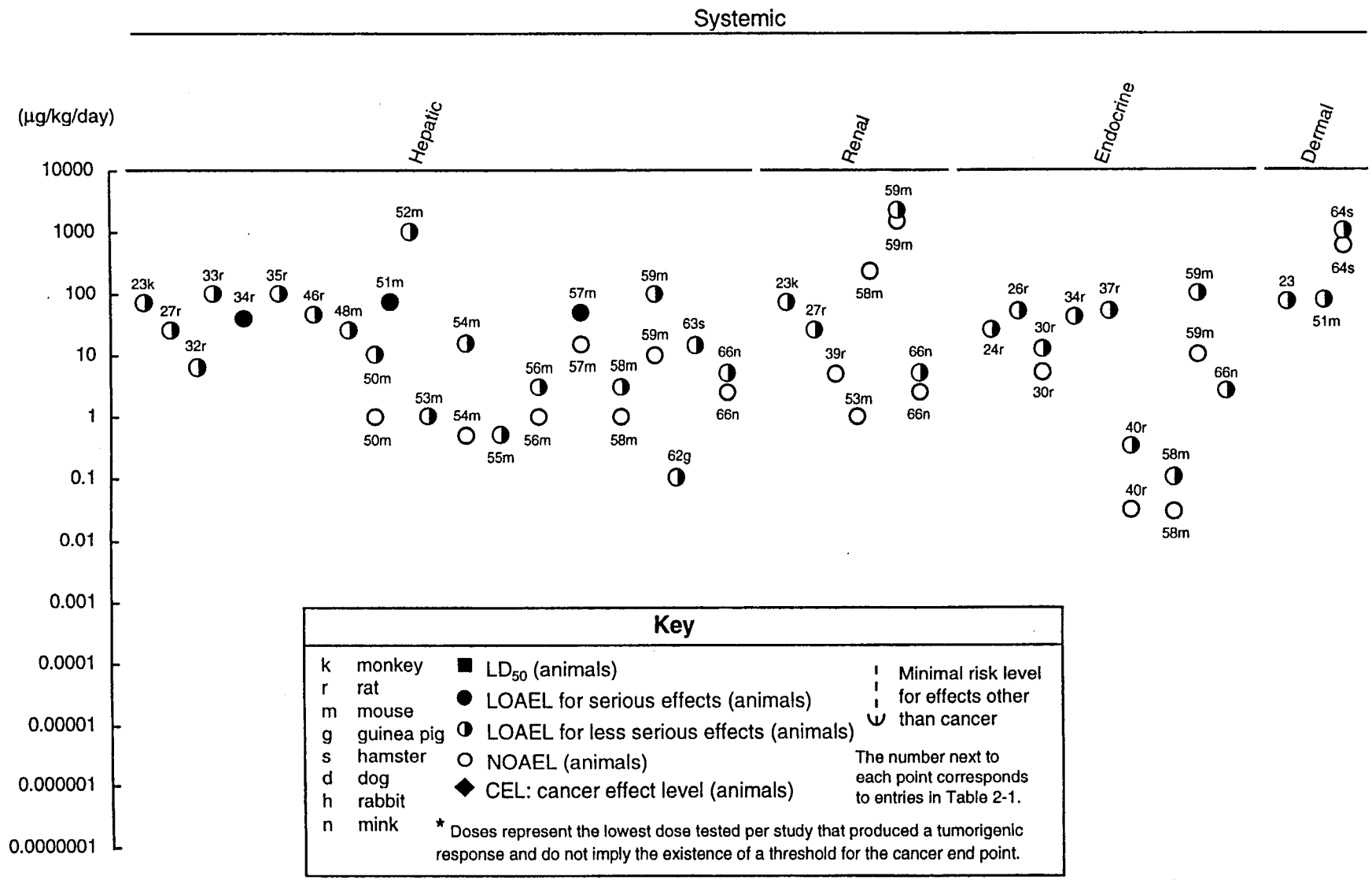


Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Acute (≤14 days)



Key

k	monkey
r	rat
m	mouse
g	guinea pig
s	hamster
d	dog
h	rabbit
n	mink

■ LD_{50} (animals)
● LOAEL for serious effects (animals)
◑ LOAEL for less serious effects (animals)
○ NOAEL (animals)
◆ CEL: cancer effect level (animals)

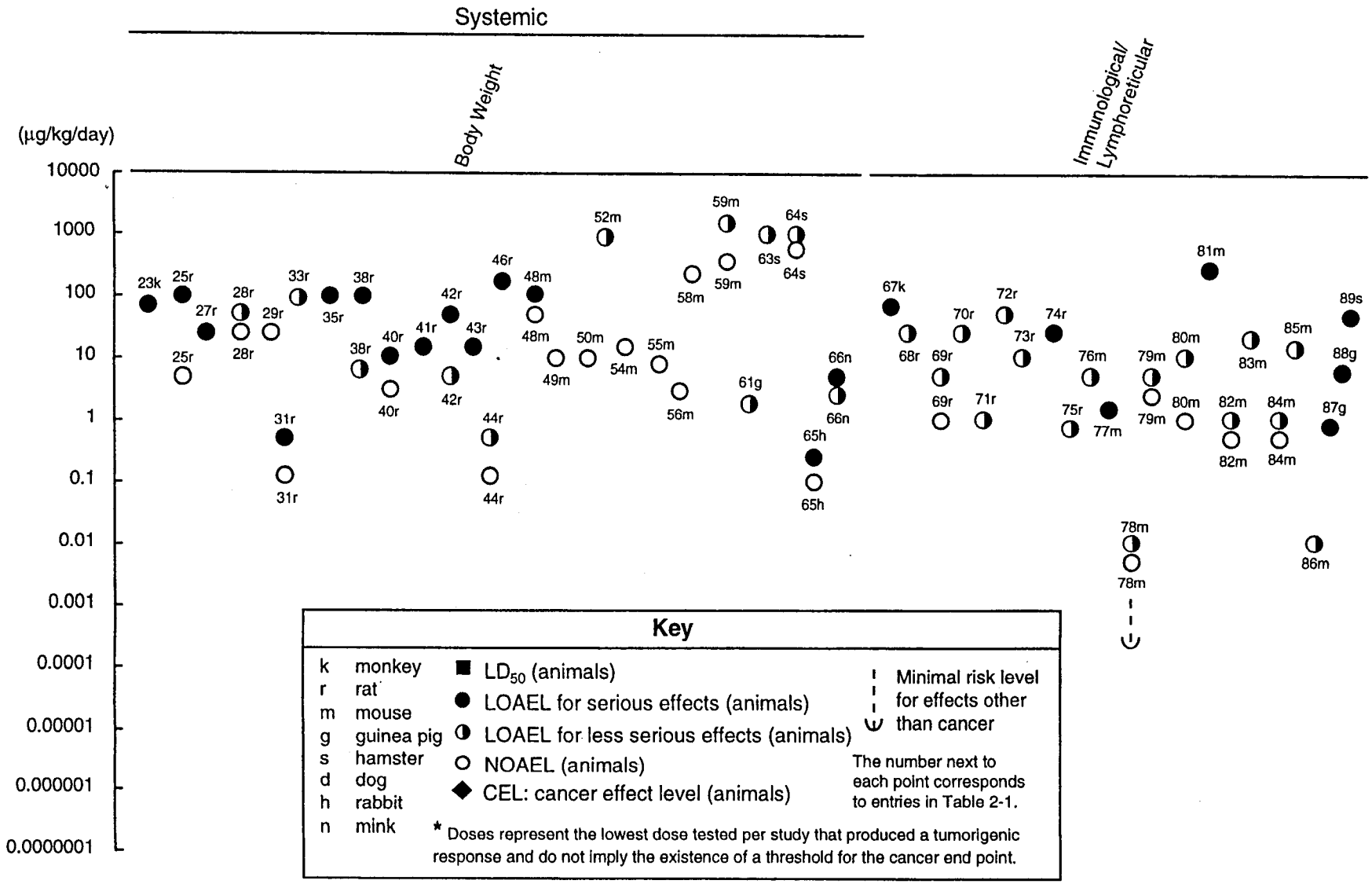
Minimal risk level for effects other than cancer

The number next to each point corresponds to entries in Table 2-1.

* 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.

Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Acute (≤14 days)



Key

k	monkey	■ LD_{50} (animals)	Minimal risk level for effects other than cancer
r	rat	● LOAEL for serious effects (animals)	
m	mouse	◑ LOAEL for less serious effects (animals)	The number next to each point corresponds to entries in Table 2-1.
g	guinea pig	○ NOAEL (animals)	
s	hamster	◆ CEL: cancer effect level (animals)	
d	dog		
h	rabbit		
n	mink		

* 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.

Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Acute (≤14 days)

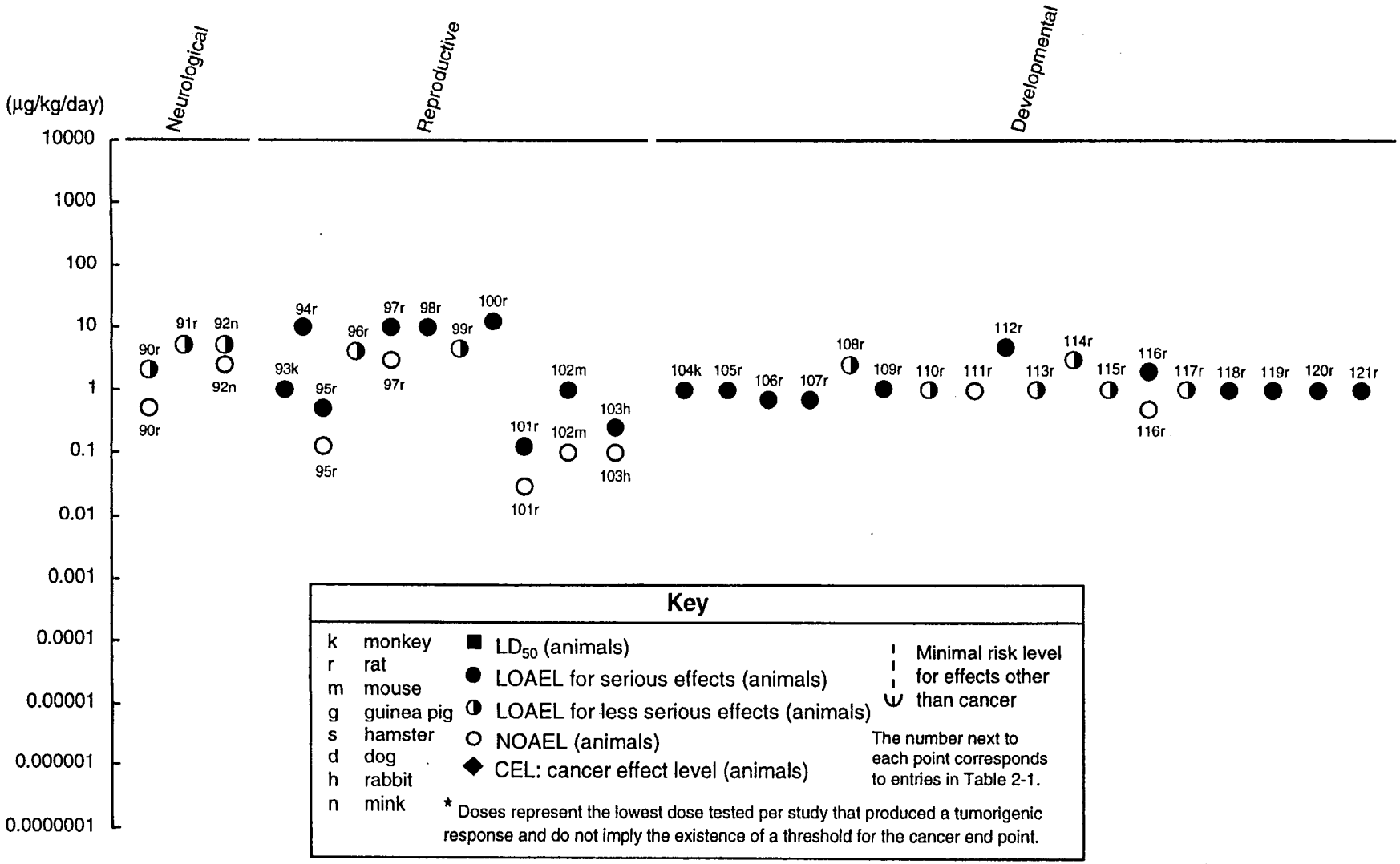


Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Acute (≤14 days)

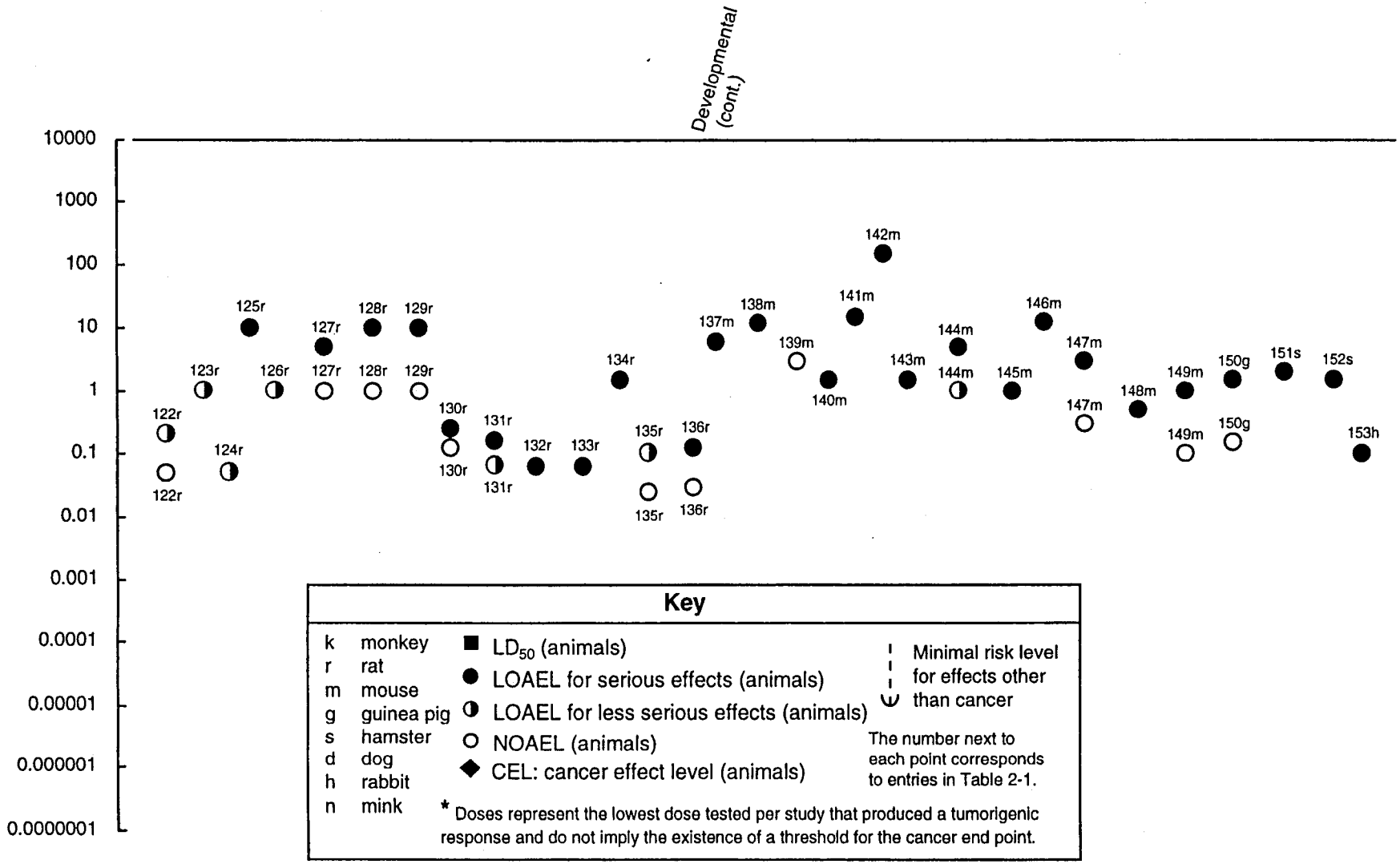


Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Intermediate (15-364 days)

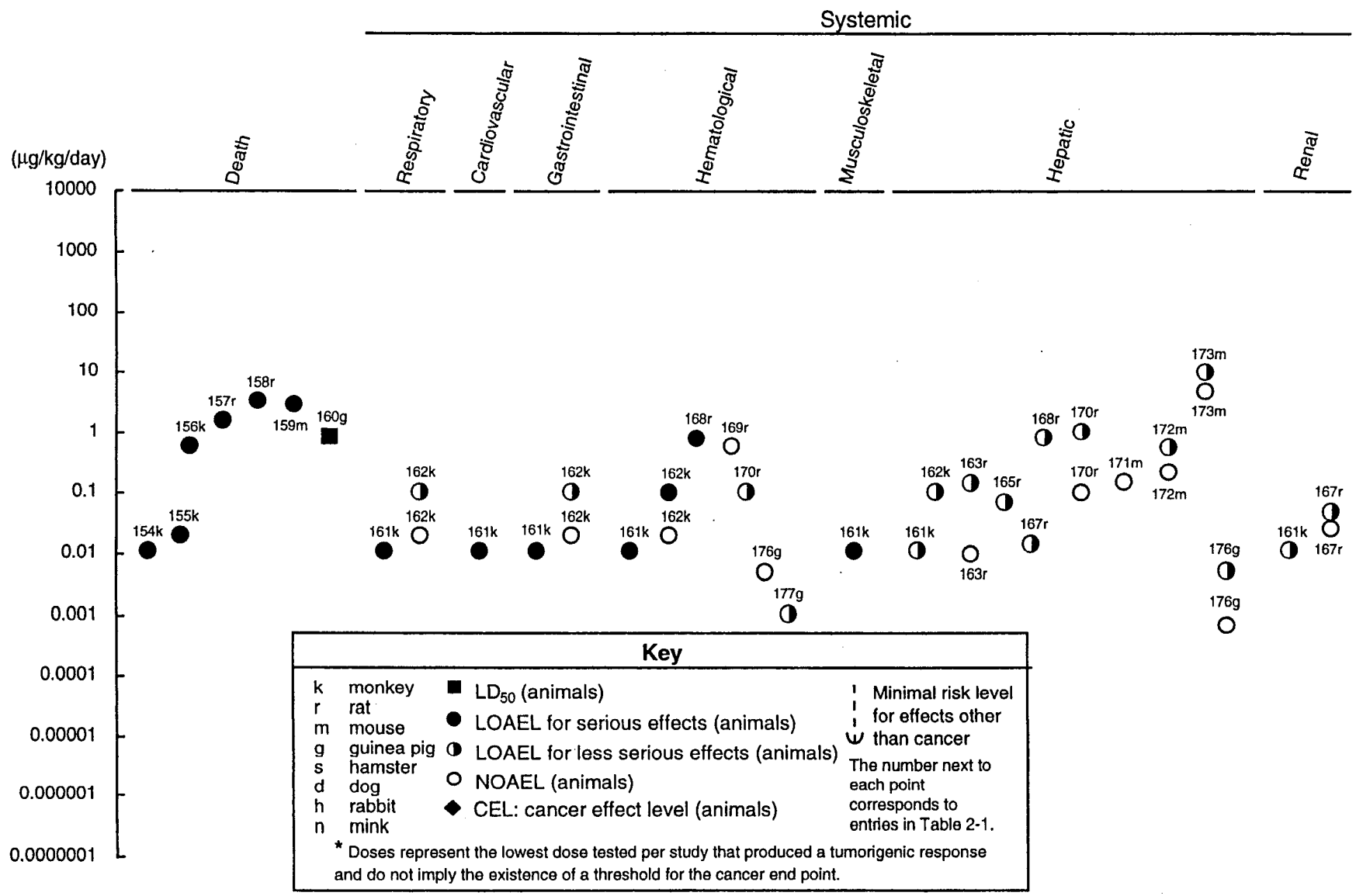


Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Intermediate (15-364 days)

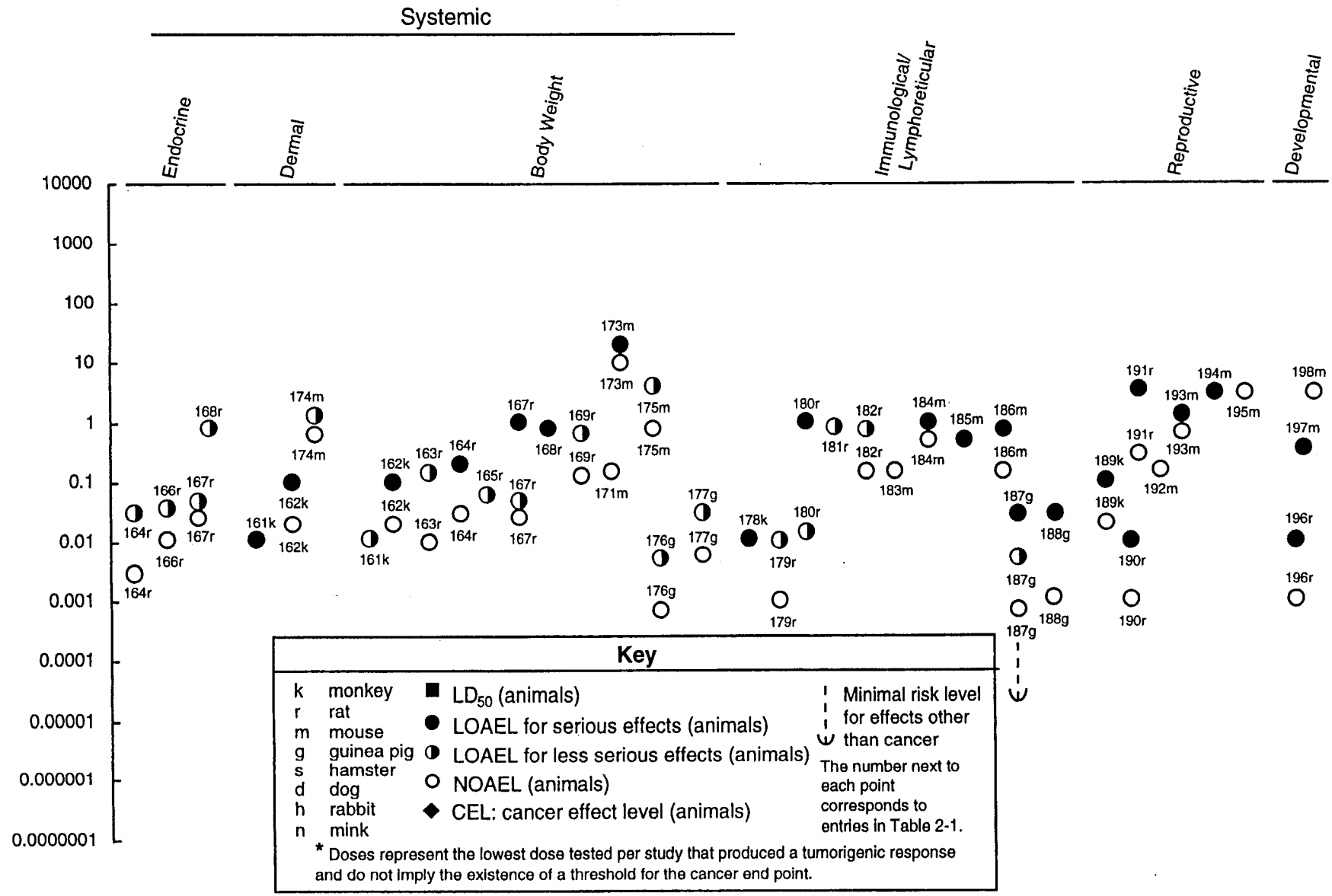


Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Chronic (≥365 days)

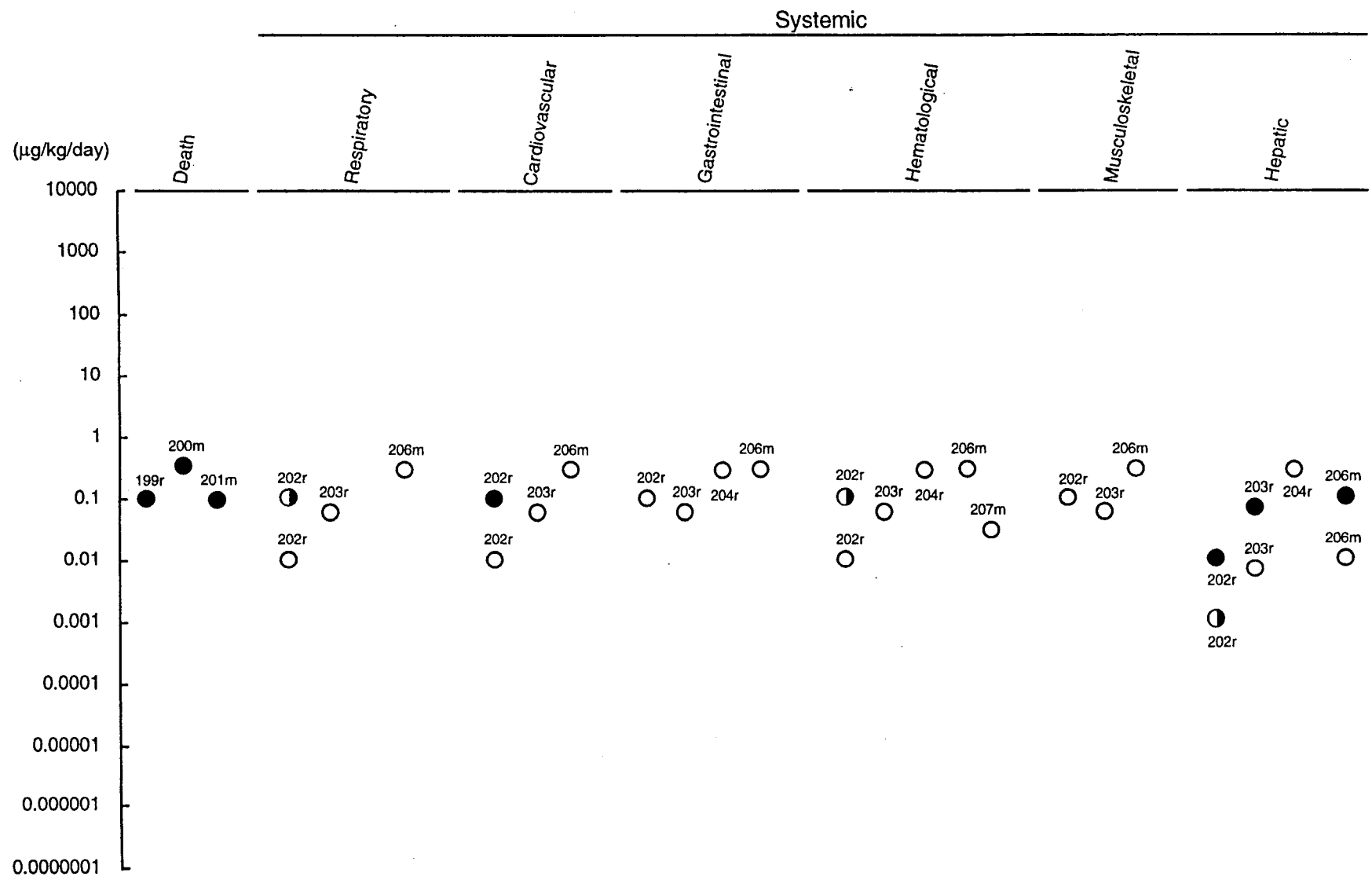


Figure 2-1. Levels of Significant Exposure to 2,3,7,8-TCDD - Oral (cont.)

Chronic (≥365 days)

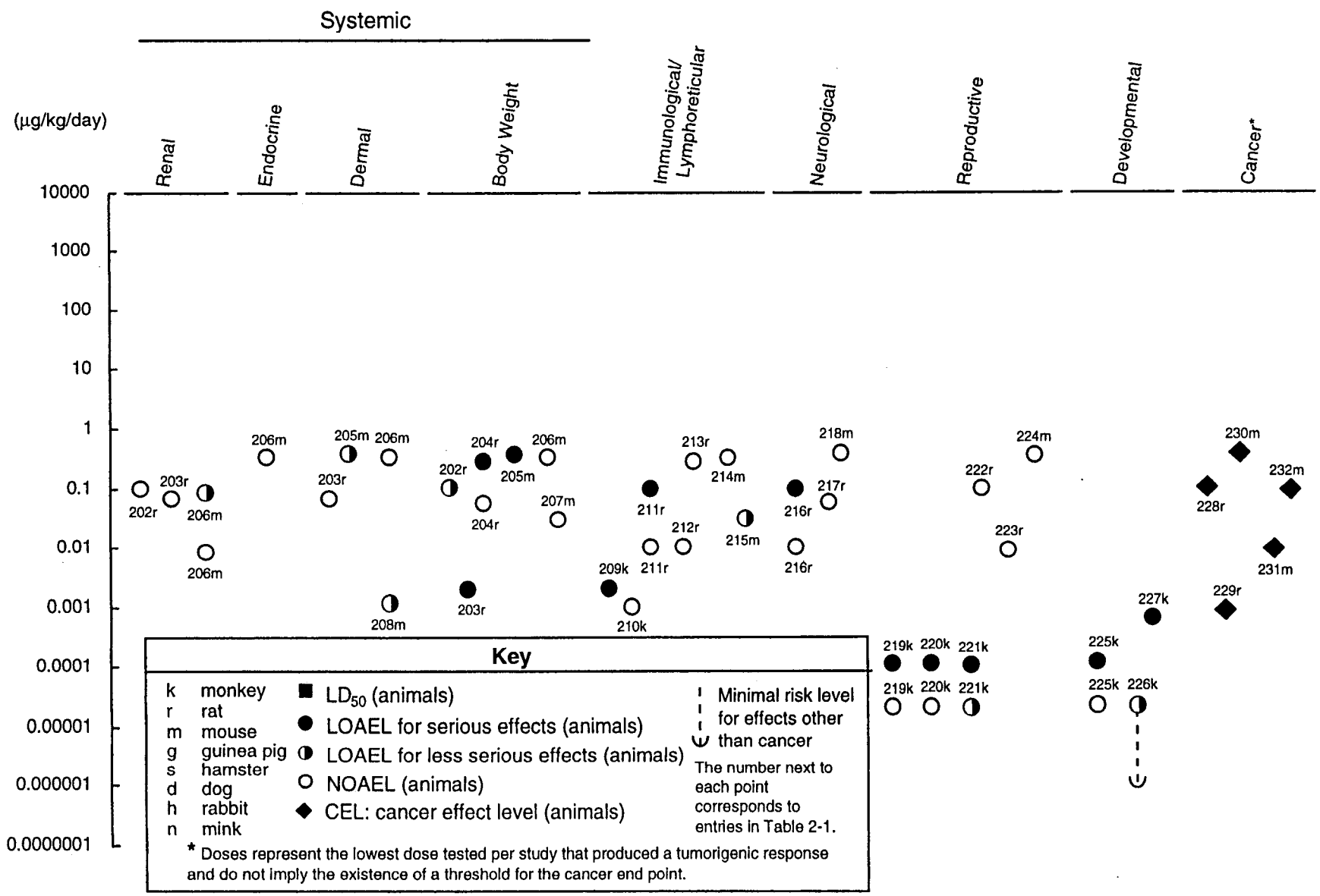


Table 2-3 Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Osborne-Mendel)	once (GO)				1800 M (LD_{50})	NCI/NTP 1980a HCDD1
						800 F (LD_{50})	
2	Rat (Sprague-Dawley)	1 d 4 x/d (GO)				6325 (LD_{50})	Stahl et al. 1992 HpCDD
3	Rat (Sprague-Dawley)	once (GO)				206 M (LD_{50})	Stahl et al. 1992 PCDD1
4	Rat (Sprague-Dawley)	1 d 2 x/d (GO)				887 (LD_{50})	Stahl et al. 1992 HCDD2
5	Mouse (C57BL/6N)	once (GO)				825 M (LD_{50})	McConnell et al. 1978 HCDD2
6	Mouse (C57BL/6N)	once (GO)				337.5 M (LD_{50})	McConnell et al. 1978 PCDD1
7	Mouse (B6C3F1)	once (GO)				750 M (LD_{50})	NCI/NTP 1980 HCDD1
						500 F (LD_{50})	

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
8	Gn pig (Hartley)	once (GO)				1125 M (LD_{50})	McConnell et al. 1978 PCDD2
9	Gn pig (Hartley)	once (GO)				60 M (LD_{50})	McConnell et al. 1978 HCDD3
10	Gn pig (Hartley)	once (GO)				600 M (LD_{50})	McConnell et al. 1978b HpCDD
11	Gn pig (Hartley)	once (GO)				72.5 M (LD_{50})	McConnell et al. 1978b HCDD2
12	Gn pig (Hartley)	once (GO)				3.1 M (LD_{50})	McConnell et al. 1978b PCDD1
13	Gn pig (Hartley)	once (GO)				29444 M (LD_{50})	McConnell et al. 1978b TrCDD
14	Gn pig (Hartley)	once (GO)				70 M (LD_{50})	McConnell et al. 1978b HCDD4
	Systemic						
15	Rat (Fischer- 344)	2 wk 5 d/wk 1 x/d (GO)	Hemato	50 M			Couture et al. 1988 OCDD
			Hepatic	50 M			

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference Chemical Form
16	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)	Hepatic	10 F	100 F (pale livers)		Schwetz et al. 1973 HCDD5
			Bd Wt	1 F		10 F (39% decreased maternal weight gain)	
17	Mouse (CD-1)	14 d 1 x/d (GO)	Bd Wt	1000 F			Courtney 1976 OCDD
18	Mouse (CD-1)	14 d 1 x/d (GO)	Bd Wt	1000 F			Courtney 1976 DCDD1
19	Mouse (CD-1)	10 d Gd 7-16 1 x/d	Hepatic	1000 F			Courtney 1976 TCDD, 1234
			Other	1000 F			
20	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GO)	Hepatic	20			Courtney 1976 OCDD
21	Mouse	14 d 1 x/d (GO)	Hepatic	10 F			Holsapple et al. 1986 DCDD1
	Immunological/Lymphoreticular						
22	Mouse (B6C3F1)	14 d 1 x/d (GO)				0.1 F (suppressed antibody response)	Holsapple et al. 1986 DCDD1

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference Chemical Form
23	Mouse (B6C3F1)	14 d 1 x/d (GO)		10 F			Holsapple et al. 1986 OCDD
24	Mouse (C57B1/6)	once (GO)				33 (decreased splenic antibody response)	Kerkvliet and Brauner 1987 HpCDD
25	Mouse (B6C3F1)	14 d 1 x/d (GO)		0.1 F	1.0 F (suppressed serum complement activity)		White et al. 1986 HCDD4
	Reproductive						
26	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		2000 F			Khera and Ruddick 1973 MCDD
27	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		2000 F			Khera and Ruddick 1973 DCDD1
28	Rat (Wistar)	10d Gd 6-15 1 x/d (GO)		2000 F			Khera and Ruddick 1973 DCDD1
29	Rat (Wistar)	110 d Gd 6-15 1 x/d (GO)		800 F			Khera and Ruddick 1973 TCDD

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)		Reference Chemical Form
30	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		5000000 F				Schwetz et al. 1973 OCDD
31	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		100000 F				Schwetz et al. 1973 DCDD1
32	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		1		10 F	(25% increased resorption)	Schwetz et al. 1973 HCDD5
	Developmental							
33	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		800				Khera and Ruddick 1973 TCDD
34	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		1000		2000	(edematous separation of cardiac myofibrils in fetuses)	Khera and Ruddick 1973 DCDD1
35	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		2000				Khera and Ruddick 1973 MCDD

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (ug/kg/day)		Serious (ug/kg/day)		
36	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		2000					Khera and Ruddick 1973 DCDD2
37	Rat (Wistar)	Gd 16 (G)			0.5	(induced microsomal enzyme activity, decreased thymus weight)			Madsen and Larsen 1989 PCDD1
38	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		0.1	1	(subcutaneous edema)	10	(growth retardation, dilated renal pelvis, delayed ossification)	Schwetz et al. 1973 HCDD5
39	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		100000					Schwetz et al. 1973 DCDD1
40	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		100000	500000	(subcutaneous edema)			Schwetz et al. 1973 OCDD
41	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GO)		20					Courtney 1976 OCDD
42	Mouse (CD-1)	10 d Gd 7-16 1 x/d		1000					Courtney 1976 TCDD

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
43	Rat (Sprague-Dawley)	13 wk 1 x/2 wk (GO)				73 M (3/20 died; first death on day 41)	Viluksela et al. 1994 HpCDD
44	Rat (Sprague-Dawley)	13 wk (GO)				2.6 F (15/20 died during treatment period; first death on day 16)	Viluksela et al. 1998a,1998b PCDD1
45	Rat (Sprague-Dawley)	13 wk (GO)				10.3 F (5/20 died during treatment period; first death on day 61)	Viluksela et al. 1998a,1998b HCDD2
	Systemic						
46	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)	Hemato		50 (mild anemia)		Birnbaum et al. 1989 OCDD
			Hepatic		50 (liver hypertrophy, enzyme induction)		
47	Rat (Fischer- 344)	4-13 wk 5 d/wk 1 x/d (GO)	Hemato		50 M (increased lymphocytes, decreased MCH, MCV, HGB)		Couture et al. 1988 OCDD
			Hepatic		50 M (cytoplasmic vacuolization)		

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference Chemical Form
48	Rat	13 wk 1 d/wk 1 x/d (GO)	Hemato	1.4	7.1 (splenic hyperplasia)		NCI/NTP 1980 HCDD1
			Hepatic	0.36	0.71 (unspecified moderate hepatoxicity)		
			Bd Wt	0.36	0.71 (13-18% decreased weight gain)		
49	Rat (Sprague-Dawley)	13 wk 1 x/2 wk (GO)	Hemato	24 M	73 M (decrease in platelet count)		Viluksela et al. 1994 HpCDD
			Hepatic	0.3 M	4 M (increased relative liver weight and EROD activity)		
			Endocr	4 M	24 M (decrease in serum total T4)		
			Bd Wt	24 M	73 M (13% decrease in body weight gain)	110 M (48% decrease in body weight gain)	

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (ug/kg/day)	Serious (ug/kg/day)	
50	Rat (Sprague-Dawley)	13 wk (GO)	Hemato		2.6 F (decreased hematocrit; reduced platelet count)		Viluksela et al. 1998a,1998b PCDD1
			Hepatic		2.6 F (decreased liver PEPCK and increased EROD activities)		
			Endocr		3.8 M (69% decrease in serum T4)		
			Dermal		2.6 F (occasional hair loss; sores in ears, nose, neck, tail, and feet)		
			Bd Wt		2.6 F (body weight reduced 18% relative controls at the end of dosing period)	3.8 M (body weight reduced by 27% relative to controls at the end of dosing period)	

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference Chemical Form
51	Rat (Sprague-Dawley)	13 wk (GO)	Hemato		10.3 F (decreased hematocrit; reduced platelet count)		Viluksela et al. 1998a,1998b HCDD2
			Hepatic		10.3 F (decreased liver PEPCK and TdO activities and increased EROD activity)		
			Endocr		15.4 M (69% decrease in serum T4)		
			Dermal		10.3 F (occasional hair loss; sores in ears, nose, neck, tail, and feet)		
			Bd Wt	10.3 F		15.4 M (body weight reduced by 24% relative to controls at the end of dosing period)	
52	Mouse	13 wk 1 d/wk 1 x/d (GO)	Hepatic	0.71	1.4 (mild hepatoxicity)		NCI/NTP 1980a HCDD1
			Bd Wt		0.18 (13-17% decreased weight gain)		
	Immunological/Lymphoreticular						
53	Rat	13 wk 1 d/wk 1 x/d (GO)		1.4	7.1 (splenic hyperplasia)		NCI/NTP 1980 HCDD1

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference Chemical Form
54	Rat (Sprague-Dawley)	13 wk 1 x/2 wk (GO)		0.3 M	4 M (decrease in absolute and relative thymus weight)		Viluksela et al. 1994 HpCDD
	CHRONIC EXPOSURE						
	Systemic						
55	Rat (Osborne-Mendel)	110 wk 7 d/wk (F)	Resp	500000			NCI/NTP 1979a DCDD1
			Cardio	500000			
			Gastro	500000			
			Hemato	500000			
			Musc/skel	500000			
			Hepatic		250000	(fatty changes)	
			Renal	500000			
			Dermal	500000			
			Bd Wt		250000	(17% decreased body weight gain)	

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (ug/kg/day)		Serious (ug/kg/day)		
56	Rat (Osborne-Mendel)	104 wk 2 d/wk (GO)	Resp		0.18	(adenomatous hyperplasia of the lungs)			NCI/NTP 1980a HCDD1
			Cardio	0.7					
			Gastro	0.7					
			Hemato	0.7					
			Musc/skel	0.7					
			Hepatic				0.18	(toxic hepatitis)	
			Renal	0.7					
			Dermal	0.7					
			Bd Wt				0.18	(38% decreased weight gain)	

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL Less Serious (ug/kg/day)	LOAEL Serious (ug/kg/day)	Reference Chemical Form
57	Mouse (B6C3F1)	90 wk 7 d/wk (F)	Resp	1300000			NCI/NTP 1979a DCDD1
			Cardio	1300000			
			Gastro	1300000			
			Hemato	1300000			
			Musc/skel	1300000			
			Hepatic			650000 (toxic hepatitis)	
			Renal	1300000			
			Dermal	1300000			
			Bd Wt		650000 (16% decreased body weight gain)		
58	Mouse (B6C3F1)	104 wk 2 d/wk (GO)	Resp	1.4			NCI/NTP 1980a HCDD1
			Cardio	1.4			
			Gastro	1.4			
			Hemato	1.4			
			Musc/skel	1.4			
			Hepatic			0.7 (toxic hepatitis)	
			Renal	1.4			
			Dermal	1.4			
			Bd Wt	1.4			

Table 2-3. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ug/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (ug/kg/day)	Serious (ug/kg/day)		
	Cancer							
59	Rat (Osborne-Mendel)	104 wk 2 d/wk (GO)				0.34	(CEL: hepatocellular carcinoma or liver neoplastic nodules)	NCI/NTP 1980a HCDD1
60	Mouse (B6C3F1)	90 wk 7 d/wk (F)				650000 M	(CEL: hepatocellular carcinoma or adenoma, lymphoma, leukemia, hemangiosarcomas)	NCI/NTP 1979a DCDD1
61	Mouse (B6C3F1)	104 wk 2 d/wk (GO)				0.7 M	(CEL: hepatocellular adenoma or carcinoma)	NCI/NTP 1980 HCDD

[a]The number corresponds to entries in Figure 2-2.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); DCDD1 = 2,7-dichlorodibenzo-p-dioxin; DCDD2 = 2,3-dichlorodibenzo-p-dioxin; Endocr = endocrine; EROD = ethoxyresorufin-O-deethylase; F = female; (F) = food; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; (GO) = gavage in oil; HCDD1 = mixture of 1,2,3,7,8,9- and 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin; HCDD2 = 1,2,3,4,7,8-hexachlorodibenzo-p-dioxin; HCDD3 = 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin; HCDD4 = 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin; HCDD5 = unspecified mixture of hexachlorodibenzo-p-dioxins; Hemato = hematological; HGB = hemoglobin; HpCDD = 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MCDD = 2-monochlorodibenzo-p-dioxin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; OCDD = octachlorodibenzo-p-dioxin; PCDD1 = 1,2,3,7,8-pentachlorodibenzo-p-dioxin; PCDD2 = 1,2,4,7,8-pentachlorodibenzo-p-dioxin; RBC = red blood cell; Resp = respiratory; TCDD = 1,2,3,4-tetrachlorodibenzo-p-dioxin; TrCDD = 2,3,7-trichlorodibenzo-p-dioxin; wk = week(s); x = times

Figure 2-2. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral

Acute (≤14 days)

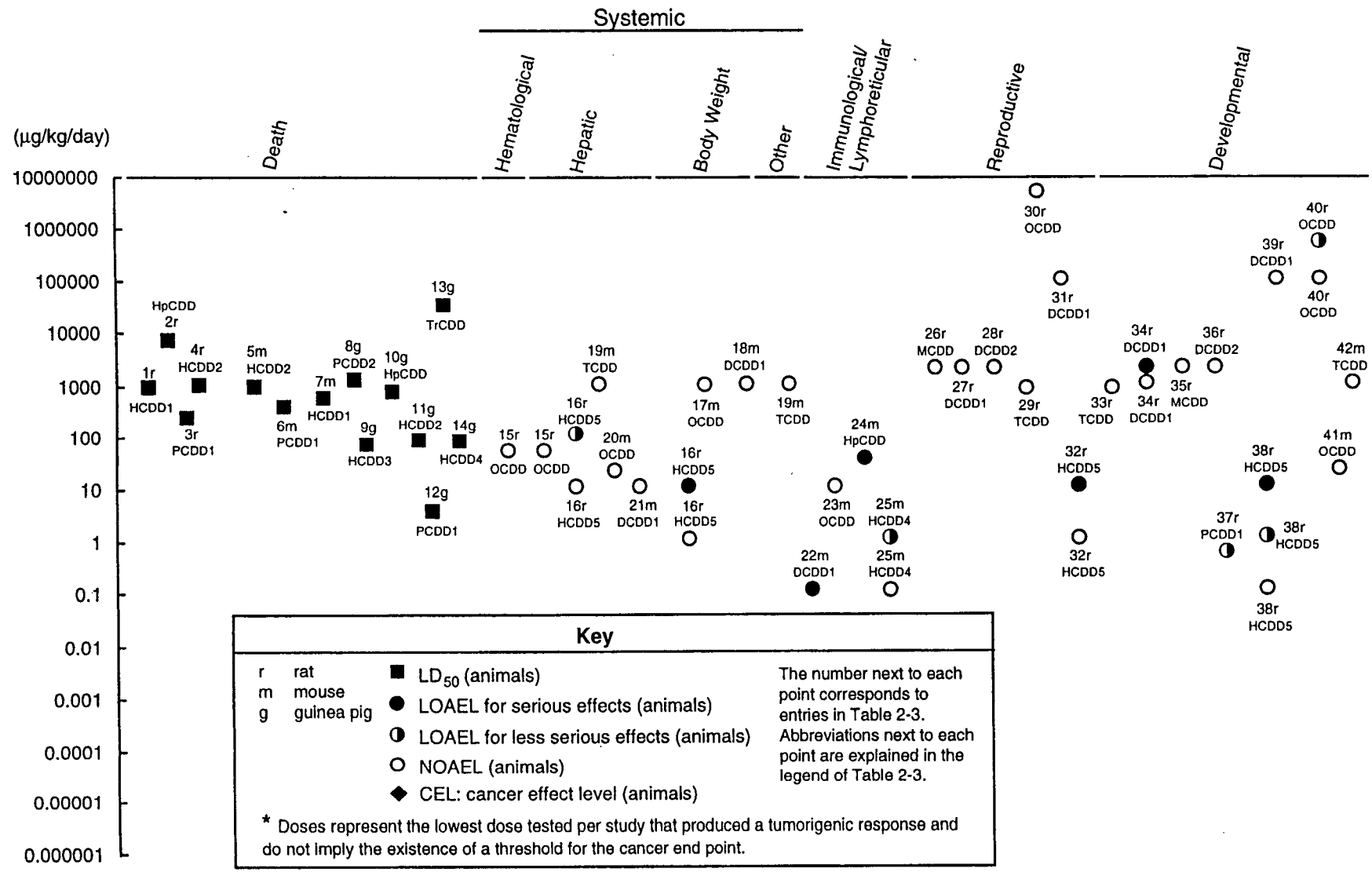


Figure 2-2. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (cont.)

Intermediate (15-364 days)

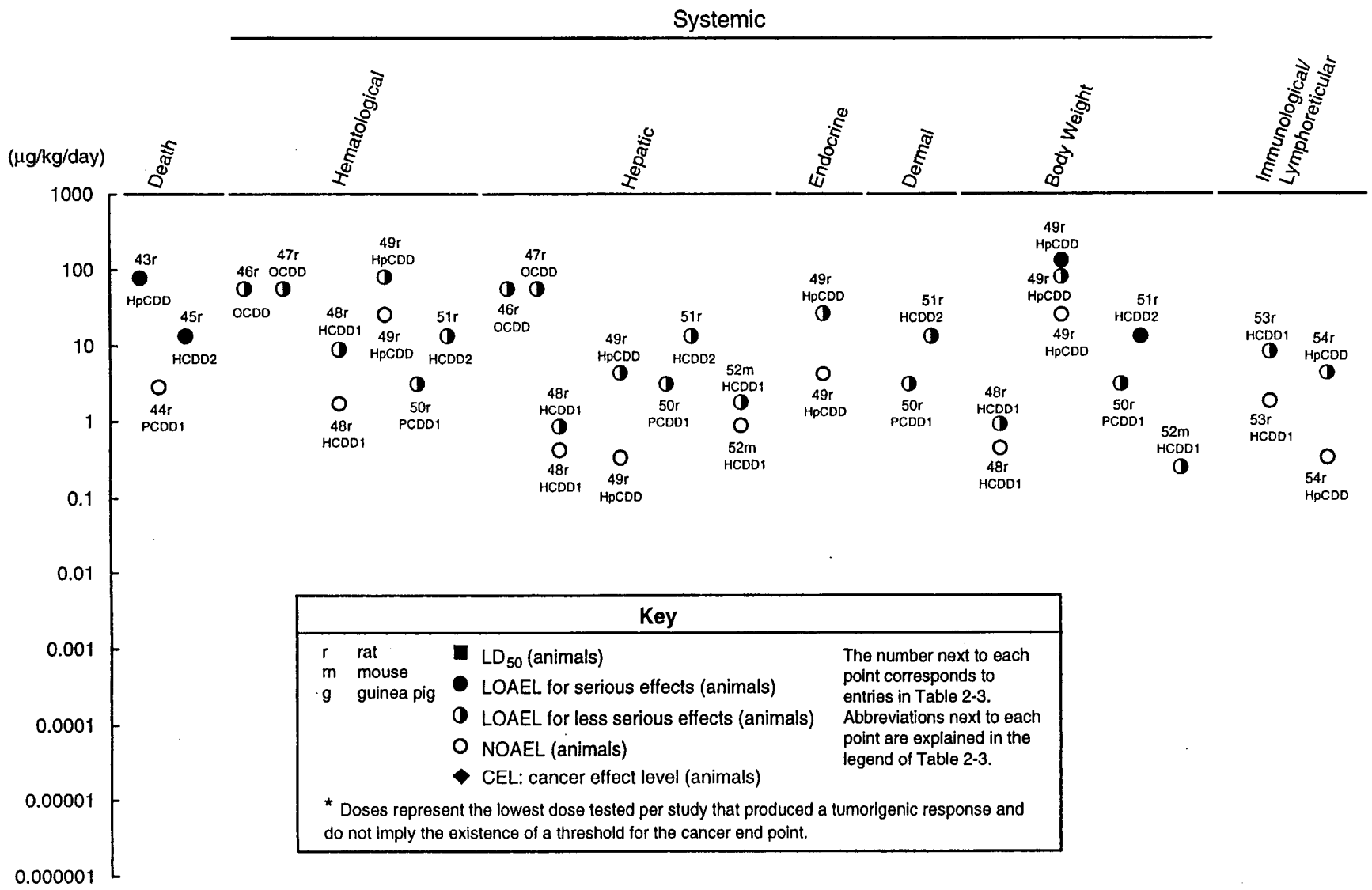
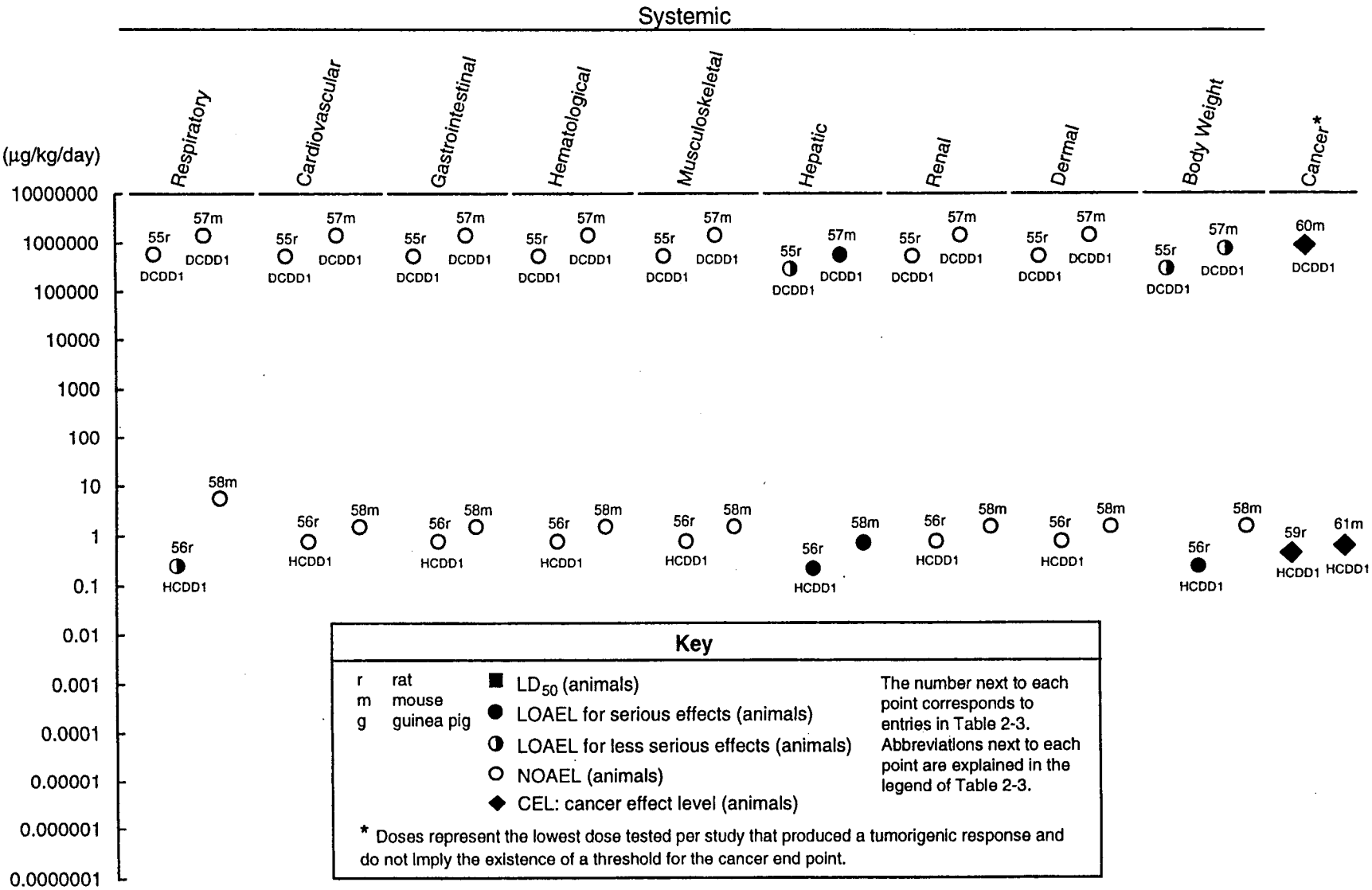


Figure 2-2. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Oral (cont.)

Chronic (≥365 days)



Similarly, no respiratory effects were found in rats and mice chronically exposed by diet to 5×10^5 and 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively (NCI/NTP 1979a). In contrast, rats exposed chronically by gavage to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD at 0.18, 0.34, and 0.7 µg/kg/day had a dose-related increased incidence of adenomatous hyperplastic lesions in terminal bronchioles and adjacent alveoli of both males and females; no such effects were found in mice exposed chronically to 0.7 µg/kg/day of that same mixture (NCI/NTP 1980). The existing information suggests that in animals, the respiratory system is not a sensitive target for CDDs toxicity via oral exposure.

Cardiovascular Effects. Cardiovascular effects have been detected in animals following acute-, intermediate-, and chronic-duration oral exposure to 2,3,7,8-TCDD. These included changes in heart weight, pathophysiological effects, and degenerative changes. However, exposures at or near a lethal dose were required to elicit these effects.

Decreased absolute heart weight was reported in minks 28 days after a single oral dose of 5 µg/kg, but not at 2.5 µg/kg (Hochstein et al. 1988). A reduction of absolute heart weight which is attributed to weight loss was also found in monkeys at 70 µg/kg (relative heart weight was increased) (McConnell et al. 1978a). Histological examinations of the heart were normal in the monkeys. This examination was not performed in minks. Doses in both species were near the lethal dose.

Kelling et al. (1987) assessed the effects of 2,3,7,8-TCDD on cardiac function tests in male Sprague-Dawley rats 7 days after single oral doses of 6.25, 25, or 100 µg/kg. At 100 µg/kg (near-lethal dose), an increased sensitivity to the inotropic (left atrium) and chronotropic (right atrium) effects of isoproterenol were observed. Three daily oral doses of 40 µg/kg caused decreased heart rate, depressed blood pressure, and increased myocardial peroxidase activity in rats (Hermansky et al. 1988). All of these effects may have been secondary to the modulation of adenylate cyclase activity at β-adrenergenic receptors as a result of hypothyroidism (Hermansky et al. 1987).

In intermediate-duration experiments, monkeys that died after exposure to diets providing 0.011 µg/kg/day of 2,3,7,8-TCDD (lethal dose) had hemorrhages in the epicardium, myocardium, and endocardium (Allen et al. 1977). Myocardial degenerative changes and periarteritis were reported in Sprague-Dawley rats chronically exposed to a diet providing a lethal dose of 0.1 µg/kg/day of 2,3,7,8-TCDD, but not in those receiving 0.01 µg/kg/day (Kociba et al. 1978a). In contrast, no histopathological lesions were observed in

the hearts of rats and mice chronically exposed by gavage to approximately 0.071 and 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively (NTP 1982b).

No histopathological lesions were observed in the hearts of rats and mice chronically exposed in the diet to 5×10^5 and 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively (NCI/NTP 1979a); or exposed for 104 weeks by gavage to approximately 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively (NCI/NTP 1980).

Gastrointestinal Effects. One of the major 2,3,7,8-TCDD-induced effects in various animal species is the wasting syndrome and hypophagia which occur after a single near-lethal dose or after repeated dosing (discussed under Body Weight Effects). Studies of effects on the gastrointestinal system have been carried out to investigate the mechanism of this starvation-like syndrome. Ulceration of the gastrointestinal tract and bloody stools were observed in minks after a single oral exposure to 5 µg 2,3,7,8-TCDD/kg (3 of 4 mink died) but not at a dose of 2.5 µg/kg/day. The response of the antral mucosa of the rat stomach to 2,3,7,8-TCDD has been studied by Theobald et al. (1991). In Sprague-Dawley rats, a single oral dose of 100 µg 2,3,7,8-TCDD/kg caused a 7–10-fold increase in serum gastrin (secreted by G-cells in the antrum) that was not detected until 14 days after dosing, whereas control rats fed a restricted diet had atrophic changes in the antral mucosa and no increase in gastrin (Theobald et al. 1991). The number of G-cells in the antral mucosa was not affected by treatment with 2,3,7,8-TCDD or paired-feed restriction, indicating that hypergastrinemia in treated rats is not due to reduced feed intake or antral G-cell hyperplasia. In 2,3,7,8-TCDD-treated rats, both gastrin and somatostatin (which inhibits gastrin release) levels in the antral mucosa were significantly decreased, and these changes were observed a week earlier than the hypergastrinemia. Moreover, the ED_{50} values (half maximum effect level of 2,3,7,8-TCDD) for the decrease in antral mucose content and concentration of gastrin (29 and 22 µg/kg, respectively) and somatostatin (24 and 19 µg/kg, respectively) was less than that for hypergastrinemia (46 µg/kg). This suggested that hypergastrinemia in 2,3,7,8-TCDD-treated rats is not a consequence of reduced antral levels of gastrin or somatostatin. Epithelial hyperplasia of the stomach occurred in rhesus monkeys following a single oral dose of 70 µg/kg; this response is unique to monkeys and cows and is not seen in rats, mice, or guinea pigs (McConnell et al. 1978b). Monkeys undergo a similar wasting syndrome as rodents after a single oral lethal dose. Moderate to severe ileitis, characterized by hyperplasia of the mucosal epithelium with hemorrhaging and necrosis, and peritonitis were observed in hamsters that died after oral administration of $1000 µg/kg 2,3,7,8-TCDD (Olson et al. 1980a).

Repeated dosing of rats at 3.4 µg/kg/day or higher caused gastrointestinal hemorrhaging in rats that died in a chronic oral-dosing study (Van Miller et al. 1977). Metaplasia of the gastric mucosa was found in rhesus monkeys exposed to 0.1 µg/kg/day of 2,3,7,8-TCDD for 3 weeks (McNulty 1984), and gastric ulcers developed after exposure to 0.011 µg/kg/day for 9 months in the feed (Allen et al. 1977). No gastrointestinal effects were observed in rats and mice chronically exposed by gavage to approximately 0.071and 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively (NTP 1982b) or in rats on diets that provided 0.1 µg/kg/day (Kociba et al. 1978a).

Gastrointestinal lesions were not observed following exposure of rats and mice to 5×10^5 and 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively, in the diet (NCI/NTP 1979a) or to 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, by gavage for 104 weeks (NCI/NTP 1980).

The above studies demonstrated that monkeys are more sensitive to gastrointestinal effects of 2,3,7,8-TCDD than rodents.

Hematological Effects. Hematological effects were reported in some animals following exposure to lethal or near-lethal doses of 2,3,7,8-TCDD. Increases in erythrocyte counts, hemoglobin, and hematocrit were observed 10–14 days after CD rats received a single oral dose of 10 µg/kg 2,3,7,8-TCDD. Increases in total leukocyte count and neutrophil counts, and a decrease in platelet counts were also observed, but bleeding time and megakaryocytes were not altered (Weissberg and Zinkl 1973). Reduction of germinal centers and increased hemosiderin deposits were seen histologically in the spleen of Sprague-Dawley rats after a single oral dose of 25 µg/kg (Christian et al. 1986a). Mild anemia developed in rhesus monkeys after a single oral dose of 70 µg/kg (McConnell et al. 1978a). No effects were found in minks exposed acutely to a lethal dose of 2,3,7,8-TCDD (7.5 µg/kg) (Hochstein et al. 1988) or in $B6C3F_1$ mice exposed to 1 µg/kg/day for 14 days (Holsapple et al. 1986a). Reversible changes (suppression of progenitor cells, decreases in leukocyte and lymphocyte counts) were reported in CD-1 mice at doses between 1 and 10 µg/kg 2,3,7,8-TCDD (Zinkl et al. 1973).

Hematological effects have also been reported following intermediate-duration exposures to 2,3,7,8-TCDD. Decreased white blood cell counts were reported in guinea pigs exposed by gavage to 0.008 µg/kg/day 2,3,7,8-TCDD for 8 weeks (Vos et al. 1973), but no hematological changes were observed following dietary exposure to 0.005 µg/kg/day 13 weeks (DeCaprio et al. 1986). Exposure to higher doses

(3.4 µg/kg/day or more) caused splenic atrophy in Sprague-Dawley rats that died during the first 4 weeks of exposure in a chronic-duration dietary study (Van Miller et al. 1977). In contrast, no hematological changes were found in rats exposed to 0.71 µg/kg/day of 2,3,7,8-TCDD for 6 weeks (Vos et al. 1973). One month of intermittent exposure to 0.1 µg/kg/day 2,3,7,8-TCDD induced thrombocytopenia in CD rats (Zinkl et al. 1973); exposure to 1 µg/kg/day caused increased erythrocyte counts and hemoglobin levels. Administration of 2,3,7,8-TCDD by gavage for 13 weeks to male Sprague-Dawley rats at doses equivalent to 0.8 µg/kg/day (only dose level tested) produced a significant decrease in platelet counts, and in some animals, increased prothrombin times (Viluksela et al. 1994). Anemia and bone marrow hypoplasia were observed in rhesus monkeys exposed to 0.1 µg/kg/day of 2,3,7,8-TCDD by gavage 3 days a week for 3 weeks (McNulty 1984). The changes were more severe with longer exposure; pancytopenia and bone marrow atrophy developed in monkeys exposed to 0.011 µg/kg/day (a lethal dose) in the feed for 9 months (Allen et al. 1977).

In chronic-duration studies, reduced erythrocyte counts were found in Sprague-Dawley rats at dietary doses of 0.1 µg/kg/day of 2,3,7,8-TCDD but not at 0.01 µg/kg/day (Kociba et al. 1978a). No hematological effects were observed in Osborne-Mendel rats or B6C3F_1 mice chronically exposed by gavage to approximately 0.071or 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively (NTP 1982b). Results from a more recent study showed that 2,3,7,8-TCDD administered by gavage to female C57BL/6 mice in gavage doses equivalent to approximately 0.03 µg/kg/day (0.2 µg/kg once/week) for 14–15 months produced no significant effects on the total number of circulating red or white blood cells or in white blood cell differentials (Oughton et al. 1995).

Hematological effects have been reported in some animals following exposure to other CDDs. No hematological effects were observed in rats after 2 weeks of intermittent exposure to 50 µg/kg/day OCDD (Couture et al. 1988), but increased neutrophils, decreased mean cell volume, and hemoglobin (Couture et al. 1988), and mild anemia was observed at the same exposure level after 13 weeks of intermittent exposure (Birnbaum et al. 1989a). A dose-dependent decrease in platelet counts was observed in male Sprague-Dawley rats following administration by gavage of doses equivalent to 73 or 110 µg 1,2,3,4,6,7,8-HpCDD/kg/day for 13 weeks (Viluksela et al. 1994); no such effect was observed with doses #24 µg/kg/day. Some rats administered the highest dose also showed increased prothrombin times. Administration of doses equivalent to 2.6 µg 1,2,3,7,8-PCDD/kg/day or 10.3 µg 1,2,3,47,8-HxCDD/kg/day for 13 weeks resulted in decreased hematocrit and reduced platelet count in female Sprague-Dawley rats (Viluksela et al. 1998a); these doses also caused mortality.

Splenic hyperplasia was observed in rats exposed by gavage to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD at 7.1 µg/kg/day, but not at 1.4 µg/kg/day for 13 weeks (NCI/NTP 1980). No hematological effects were observed in Osborne-Mendel rats or $B6C3F_1$ mice chronically exposed to 5×10^5 and 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively, in feed (NCI/NTP 1979a) or exposed to 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, 2 days a week for 104 weeks by gavage (NCI/NTP 1980).

The above results demonstrated hematological effects in animals following CDD exposure; however, the observed changes in the red and white blood cell counts were nonspecific and were probably due to the broad systemic toxicity of 2,3,7,8-TCDD rather than to a direct effect on the hematological system.

Musculoskeletal Effects. The musculoskeletal system does not appear to be a major target of toxicity in animals exposed to CDDs. Only one study reported hemorrhages in the musculoskeletal system of severely debilitated monkeys following dietary exposure to 0.011 µg/kg/day of 2,3,7,8-TCDD for an intermediate duration (Allen et al. 1977).

No musculoskeletal effects were observed in Sprague-Dawley rats exposed to 0.1 µg/kg/day in the diet for 2 years (Kociba et al. 1978a) or in Osborne-Mendel rats and $B6C3F_1$ mice chronically exposed 2 days a week by gavage to 0.071and 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively (NTP 1982b).

Chronic experiments with other congeners showed no musculoskeletal effects in Osborne-Mendel rats and $B6C3F_1$ mice exposed in the diet to 5×10^5 and 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively (NCI/NTP 1979a) or by gavage to approximately 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively (NCI/NTP 1980).

Hepatic Effects. Effects on the liver are seen after acute oral exposure or after intermediate and chronic exposure to CDDs. Alterations in metabolism, biochemical changes, and increases in liver weights (without histologic changes) are sensitive markers of effects, but they are not clearly overt toxic effects; they may predict a toxic or histopathologic effect that will occur at higher doses or after longer exposure. Likewise induction of mixed-function oxidases (MFO) and cytochrome P-450s are generally considered adaptive effects; they may be associated with increased liver weight, but are not necessarily associated with histopathologic changes. However, alterations in cytochrome P-450 (e.g., CYP1A1) may lead to altered metabolism and/or toxicity of other xenobiotics and endogenous compounds. Increases in liver enzymes

such as AST and ALT in serum are an indication of cell death or necrosis. Effects on the liver that occur at near-lethal doses or when animals are debilitated and approaching moribundity are secondary effects and are not specific to the action of CDDs on the liver. The liver should not be implicated as a target organ in these cases. The types of histological changes caused by CDDs and their severity vary widely between species and strains of laboratory animals and the doses administered.

Histological changes in the liver were observed after acute-, intermediate-, and chronic-duration exposures. Enlarged hepatocytes with finely vacuolated cytoplasm in the centrilobular region were observed 20 days after administration of a single oral lethal dose of 75 µg/kg 2,3,7,8-TCDD to adult Sprague-Dawley rats (Christian et al. 1986a); cellular degeneration in the centrilobular region was observed in Fischer 344 rats 20 days after a single oral dose of 1000 µg/kg (Kelling et al. 1985). Three daily doses of 40 µg/kg caused centriacinar necrosis and enlarged hepatocytes in Sprague-Dawley rats (Hermansky et al. 1988). In all the above citations, the changes were secondary to the wasting syndrome and occurred after severe weight loss. Focal areas of mild hydropic degeneration of the liver associated with increased liver weight was seen in $B6C3F_1$ mice receiving 1 µg/kg/day 2,3,7,8-TCDD for 14 days (non-lethal) (Holsapple et al. 1986a). Swelling of hepatocytes, disruption of cell membranes, and dilation of sinusoids in the central vein area of the liver accompanied by cellular necrosis were observed after a single lethal dose of 360 µg/kg in C57B46 mice (Kelling et al. 1985); central necrosis in the livers of hairless A2G hr/+ mice dosed once at 75 µg/kg was reported (Greig 1984; Greig et al. 1987). Guinea pigs only showed minimal focal necrosis at 42 days after a single oral dose of 0.1 µg/kg 2,3,7,8-TCDD (Turner and Collins 1983). Hypertrophy, steatosis, cytoplasmic degeneration, and hyaline-like cytoplasmic inclusion bodies were observed at non-lethal and lethal doses (0.5 to 20 µg/kg); no between group qualitative differences in this histological alteration were found (Turner and Collins 1983). No degenerative changes were observed by Kelling et al. (1985) prior to death in guinea pigs given a single oral lethal dose of 2 µg/kg. In minks, a sensitive species, pale and mottled livers were observed at gross necropsy 28 days after a single lethal oral dose of 5 µg/kg (Hochstein et al. 1988).

Mild-to-moderate hepatic effects were also seen after intermediate-duration exposure to 2,3,7,8-TCDD. Unspecified histopathological hepatic lesions were reported following intermittent exposure to 2,3,7,8-TCDD in female Osborne-Mendel rats at 0.07 µg/kg/day and in female $B6C3F_1$ mice at 0.7 µg/kg/day for 13 weeks (NTP 1982b). Cytomegaly with focal necrosis was observed in C57BL/6J mice exposed to 10 µg/kg/day by gavage 1 day/week for 4 weeks (Thigpen et al. 1975). Increase relative liver weight and hepatocellular inclusions were found in guinea pigs exposed to 0.005 µg/kg/day in the feed

for 90 days (DeCaprio et al. 1986); this dose level also significantly reduced serum ALT activity in females and increased triglycerides in males. Biliary epithelial hyperplasia has been reported in monkeys following exposure to lethal levels (0.011 µg/kg/day) in feed for 9 months (Allen et al. 1977) and after intermittent exposure at 0.1 µg/kg/day by oral gavage for 3 weeks (McNulty 1984).

Liver necrosis occurred in Sprague-Dawley rats that died during the first 4 weeks of dietary exposure to 2,3,7,8-TCDD at 3.4 µg/kg/day in a chronic-exposure experiment, while no non-cancerous liver effects were found in rats chronically exposed to 0.286 µg/kg/day (Van Miller et al. 1977). Toxic hepatitis characterized by lipidosis and hydropic degeneration of hepatocytes with proliferation of bile ductules and by mild fibrosis was observed in 14/50 male and 32/49 female Osborne-Mendel rats following exposure by gavage to approximately 0.071 µg/kg/day of 2,3,7,8-TCDD administered for 104 weeks and in 44/50 male $B6C3F_1$ mice receiving 0.071µg/kg/day or 34/47 female mice receiving 0.3 µg/kg/day (NTP 1982b). In addition, cytoplasmic vacuolation, hyperplasia, hepatocellular degeneration, and liver necrosis occurred in Sprague-Dawley rats chronically exposed to diets providing doses of 0.001 (females) and 0.01 (both sexes) µg/kg/day 2,3,7,8-TCDD, respectively (Kociba et al. 1978a).

Biochemical changes indicating liver effects following acute oral exposure to 2,3,7,8-TCDD included hypoglycemia and increased serum triglycerides and cholesterol 10 days after a single sublethal oral dose of 45 µg/kg in Fischer 344 rats (Walden and Schiller 1985); earlier, Albro (1978) found increased triglycerides and decreased sterol esters after a non-lethal dose of 2,3,7,8-TCDD and increased cholesterol and free fatty acids after a lethal dose. Reduced retinol storage in the liver was found in Sprague-Dawley rats exposed to a single dose of 1 µg/kg 2,3,7,8-TCDD (Thunberg 1984). Reduction of hepatic retinol by 2,3,7,8-TCDD was greater (87%) in younger rats with lower initial weights (Thunberg et al. 1984) than in more mature rats (60%) (Thunberg et al. 1979, 1980). Significant and maximum induction of hepatic ethoxyresorufin-O-deethylase (EROD, marker for CYP1A1 activity) activity and dose-related decrease in liver phosphoenolpyruvate carboxykinase (PEPCK, a key enzyme of gluconeogenesis) was observed in female Long Evans rats 4 days after a single gavage dose of 5.3–60 µg 2,3,7,8-TCDD/kg (Fan and Rozman 1995). Hepatic activity of tryptophan 2,3-dioxygenase (TdO, a key enzyme of tryptophan metabolism) was elevated by 2,3,7,8-TCDD-treatment (significantly at 5.3, 12, and 18 µg/kg but not 60 µg/kg), whereas serum tryptophan levels were not altered. EROD activity had diminished considerably 90 days after dosing, although it was still 10 times the control values, and PEPCK and TdO activities had returned to control values. The authors concluded that gluconeogenesis is inhibited by 2,3,7,8-TCDD in Long Evans rats by reducing liver PEPCK activity (Fan and Rozman 1995).

Hepatic porphyria has been found after acute oral dosage of mice with 2,3,7,8-TCDD. A single oral dose of 150 µg/kg or 4 weekly doses of 25 µg/kg caused an accumulation of porphyrins and induction of delta aminolevulinic acid synthetase in $B6C3F_1$ mice (Goldstein et al. 1973). These were lethal doses and caused severe histologic liver damage. Single oral doses as high as 30 µg/kg did not produce porphyria acutely or within 16 weeks (Goldstein 1982). Elevation of serum levels of ALT and sorbitol dehydrogenase, which are indicative of subclinical toxic effects on the liver, have been found in mice after a single oral non-lethal dose (Greig 1984; Rosenthal et al. 1989; Smith et al. 1981). Smith et al. (1981) compared the sensitivity of C57BL/10 mice and DBA/2 mice, and found that the DBA/2 mouse was 20 times less sensitive than the C57 strain to 2,3,7,8-TCDD-induced porphyria. Recent results from Weber et al. (1995) suggested that acute toxicity of 2,3,7,8-TCDD occurs between 37.5 and 235 µg/kg in male C57BL/6J mice and between 375 and 3,295 µg/kg in male DBA/2J mice, as judged by decreases in liver PEPCK and glucose-6-phosphatase (G-6-Pase, also a key enzyme of gluconeogenesis) activities, reduction in blood glucose, and changes in relative liver weight 8 days after a single gavage dose of 2,3,7,8-TCDD. The ED_{50} for induction of hepatic EROD activity in male C57BL/6J mice was estimated at 1.1 µg/kg compared with 16 µg/kg in DBA/2J mice. Also there was no evidence of a reduction of liver TdO activity or of elevation of serum tryptophan levels over the dose range tested (0.03–235 µg/kg in C57BL/6J mice and 1–3,295 µg/kg in DBA/2J mice). Dose-dependent induction of EROD has also been observed in the liver from female $B6C3F_1$ mice after single (Diliberto et al. 1995) and repeated (DeVito et al. 1994) oral 2,3,7,8-TCDD doses. In the repeated-dosing study (DeVito et al. 1994), both EROD and acetanilide-4-hydroxylase (marker for CYP1A2) activities were induced with doses as low as 1.5 ng 2,3,7,8-TCDD/kg/day. Pegram et al. (1995) found no differences in the dose-response curves for hepatic EROD induction between young and old male C57BL/6N mice 8 days after a single dose of 0.015–15 µg 2,3,7,8-TCDD/kg. However, induction of acetanilide-4-hydroxylase was significantly greater in old than in young mice. Also a trend of greater relative liver weight with increasing dioxin dose was observed in young mice, whereas liver weight was not altered in old mice (Pegram et al. 1995).

Increased liver weights were reported in pregnant mice that received 25 µg/kg/day (Courtney 1976), 3 µg/kg/day (Smith et al. 1976), or 0.5 µg/kg/day (Silkworth et al. 1989b) for 10 days during gestation, and in monkeys receiving a single oral dose of 70 µg/kg (McConnell et al. 1978a). The ED_{50} values for liver enlargement following a single oral dose of 2,3,7,8-TCDD were calculated as 100 µg/kg 2,3,7,8-TCDD in Sprague-Dawley rats, 1,000 µg/kg in C57BL/6 mice, and 14 µg/kg in Syrian hamsters (Hanberg et al. 1989). These ED_{50} values approach and exceed the LD_{50} values for rats and mice (see Section 2.2.2.1).

In a 1-week dietary study in female Sprague-Dawley rats, a dose of 1 µg 2,3,7,8-TCDD/kg/day induced a significant increase in absolute liver weight and a lower dose of 0.32 µg/kg/day significantly increased relative liver weight (Van Birgelen et al. 1995). Other hepatic effects observed in this study included significantly dose-related increased hepatic microsomal activities of EROD and acetanilide-4-hydroxylase, beginning at the lowest dose tested (0.014 µg/kg/day), and dose-related decrease in hepatic retinol at $0.014 µg/kg/day. In agreement with the results of Van Birgelen et al. (1995), Viluksela et al. (1994) also reported increases in absolute and relative liver weights in male Sprague-Dawley rats administered 2,3,7,8-TCDD by gavage for 13 weeks at doses that supplied approximately 0.8 µg 2,3,7,8-TCDD/kg/day (the only dose level tested). An increase in liver EROD activity and decrease in liver PEPCK activity were also reported in the study. Liver TdO activity and total serum tryptophan were not significantly altered in surviving rats, but TdO activity was significantly decreased in moribund animals with signs of wasting syndrome, whereas serum tryptophan levels were doubled in these animals. Li and Rozman (1995) examined the reversibility of 2,3,7,8-TCDD-induced changes in some liver enzymes in male Sprague-Dawley rats treated by gavage with doses equivalent to 0.003–1.6 µg/kg/day for 10 weeks and allowed to recover for an additional 6-week period. As reported by others, there was a dose-dependent decrease in TdO activity with a concurrent increase in serum tryptophan levels (both significant at the highest-dose level) and a decrease in PEPCK activity (significant at $1 µg/kg/day). These dose responses were very similar to the dose response for body weight reduction. EROD was induced even at the lowest dose and maximum induction was attained at $35 µg/kg/day. After the 6-week recovery period, PEPCK and TdO activities, as well as serum tryptophan levels, returned to near-control levels; however, EROD still remained induced. The authors (Li and Rozman 1995) indicated that the results supported the hypothesis that subchronic toxicity of 2,3,7,8-TCDD is similar to its acute toxicity when the dose is corrected for pharmacokinetics. In other words, toxicity is determined by the body burden represented by the cumulative dose minus the portion of the dose already eliminated.

Hepatic effects have also been reported in animals following exposure to other CDDs. Pale, friable livers were observed in 3/20 Sprague-Dawley rat dams exposed to 100 µg/kg/day of mixed HxCDD during gestation (incidence in control group was not reported), but not in those exposed to 10 µg/kg/day (Schwetz et al. 1973). No effects on the liver were observed at 10 µg/kg/day of 2,7-DCDD in B6C3F_1 mice (Holsapple et al. 1986b), at 20 µg/kg/day of OCDD in pregnant CD-1 mice (Courtney 1976), or at 1,000 µg/kg/day of 1,2,3,4-TCDD in pregnant CD-1 mice (Courtney 1976).

Data for hepatic effects after intermediate-duration exposure to the other congeners were available for 1,2,3,7,8-PCDD, 1,2,3,4,7,8-HxCDD, a mixture of 1,2,3,7,8,9-HxCDDs and 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD. Mild hepatotoxicity (not otherwise specified) was recorded in rats exposed to 0.71 µg/kg/day of a mixture of 1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD, and in mice exposed to the same mixture by gavage for 13 weeks to 1.4 µg/kg/day (NCI/NTP 1980). No effects were seen at 0.36 µg/kg/day and at 0.71 µg/kg/day in rats and mice, respectively. Absolute liver weight was significantly increased in male Sprague-Dawley rats administered $24 µg 1,2,3,4,6,7,8-HpCDD/kg/day by gavage for 13 weeks (Viluksela et al. 1994). Relative liver weight was increased at $4 µg/kg/day. Liver activity of PEPCK was significantly decreased with the 2 highest-dose levels tested, 73 and 110 µg/kg/day, whereas hepatic EROD activity was dose-dependently induced over the dose range tested, 0.3 to 110 µg/kg/day. Liver TdO activity and serum total tryptophan were not significantly altered at #24 µg/kg/day; however, TdO was decreased and serum tryptophan was increased in rats that died at the two highest dose levels. Similar results were reported in rats treated with 1,2,3,7,8-PCDD (2–4 µg/kg/day) or 1,2,3,4,6,7-HxCDD (10–15 µg/kg/day) (Viluksela et al. 1998b). Cytoplasmic vacuolization of hepatocytes (Couture et al. 1988) and liver hypertrophy with induced hepatic enzymes (Birnbaum et al. 1989a) were reported in rats gavaged with 50 µg/kg/day OCDD 5 days a week for up to 13 weeks.

Toxic hepatitis was reported in Osborne-Mendel rats and in B6C3F_1 mice following gavage exposure to 0.18 µg/kg/day and to 0.34 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, for 104 weeks (NCI/NTP 1980). The corresponding NOAEL values are recorded in Table 2-3. Furthermore, fatty changes in the liver were found in rats chronically exposed to 2,7-DCDD at a dose of 2.5×10^5 µg/kg/day in the feed (NCI/NTP 1979a). In contrast, no liver effects were observed in mice following chronic exposure to 1.3×10^6 µg/kg/day of 2,7-DCDD in the feed (NCI/NTP 1979a).

In conclusion, the above studies demonstrated that the liver is a primary target of CDD toxicity. 2,3,7,8-TCDD was the most toxic congener, but other congeners were also capable of inducing hepatic effects. The induced effects were dose-related and species- and strain-related. It also appeared that for some hepatic end points, and after repeated dosing, toxicity is determined by the body burden represented by the cumulative dose minus the portion of the dose eliminated.

Renal Effects. Mild-to-moderate renal effects have been reported in some mature animals exposed to lethal or near-lethal levels of 2,3,7,8-TCDD. Acute exposure to 2,3,7,8-TCDD caused dilation of

convoluted tubules and Bowman's spaces at 25 µg/kg in Sprague-Dawley rats (Christian et al. 1986) and epithelial hyperplasia in the renal pelvis at 70 µg/kg in rhesus monkeys (McConnell et al. 1978a). Similar findings were reported in monkeys exposed to 0.011 µg/kg/day of 2,3,7,8-TCDD for 9 months (Allen et al. 1977). Kidney weights were not affected in male C57BL/6J and DBA/2J mice treated with a single 0.03–235 µg/kg or 1–3,295 µg/kg 2,3,7,8-TCDD dose, respectively (Weber et al. 1995). Rats administered doses of $0.047 µg/kg/day for 13 weeks exhibited an increase in relative kidney weight; a dose of 0.026 µg/kg/day was without effect (Van Birgelen et al. 1995). Chronic exposure of $B6C3F_1$ mice by gavage to approximately 0.071 µg/kg/day of 2,3,7,8-TCDD induced renal inflammatory changes; no effects were found at 0.0071 µg/kg/day (NTP 1982b). In contrast, no renal effects were found in Osborne-Mendel rats exposed to 0.071 µg/kg/day of 2,3,7,8-TCDD for 104 weeks (NTP 1982b) or in Sprague-Dawley rats exposed to 0.1 µg/kg/day of 2,3,7,8-TCDD in the feed for 2 years (Kociba et al. 1978a).

Studies with other congeners reported no renal effects following chronic exposure to 0.34 µg/kg/day and 0.7 µg/kg/day of a mixture of 1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD by gavage in rats and mice, respectively (NCI/NTP 1980) or 5×10^5 and 1.3×10^6 µg/kg/day of 2,7-DCDD in the feed in rats and mice, respectively (NCI/NTP 1979a).

The above data suggest that the observed renal effects in mature animals may be secondary to the general response to 2,3,7,8-TCDD toxicity with the exception of the epithelial hyperplasia reported in monkeys. However, developmental studies clearly show that the ureteral epithelium is altered by *in utero* exposure to CDDs as manifested by hyperplasia of ureteral lining epithelial cells leading to hydronephrosis (see Section 2.2.2.6).

Endocrine Effects. Blood corticosterone levels were decreased to 29 and 26% of control values in male Sprague-Dawley rats at 14 and 21 days after a single oral dose of 25 µg/kg 2,3,7,8-TCDD, respectively (Balk and Piper 1984). Since 11-β-hydroxyprogesterone levels were elevated, the authors suggested that 2,3,7,8-TCDD produced a block at the 21-hydroxylase step in the synthesis of corticosterone. This was directly demonstrated in a follow-up study in which the authors observed a 35% decrease in 21-hydroxylase activity 7 days after a single oral dose of 50 µg/kg 2,3,7,8-TCDD (Mebus and Piper 1986). Corticosterone serum levels from samples taken late in the light phase decreased up to 40% in male Sprague-Dawley rats administered a single 50 µg 2,3,7,8-TCDD/kg dose (DiBartolomeis et al. 1987). The effect was attributed to 2,3,7,8-TCDD-induced inhibition of cholesterol side-chain cleavage. In samples taken early in the light cycle, corticosterone levels increased 4-fold relative to controls; however,

this increase was shown to result from nutritional deprivation rather than from a direct effect of 2,3,7,8-TCDD. The possibility that altered levels of corticosterone result from a 2,3,7,8-TCDD-induced effect on adrenocorticotropin (ACTH) was examined by Bestervelt et al. (1993). ACTH serum levels were significantly increased in male Sprague-Dawley rats over a 14-day period following administration of a single dose of 50 µg 2,3,7,8-TCDD/kg; maximum increases were observed on days 3 and 14. Plasma corticosterone levels were significantly increased on days 1 and 5, but were reduced below control levels on days 10 and 14. Treatment with 2,3,7,8-TCDD did not affect the activity of the rate-limiting enzyme for adrenal steroidogenesis, mitochondrial cytochrome P-450 cholesterol side chain cleavage. Basal corticosterone concentration in adrenal glands from 2,3,7,8-TCDD-treated rats was significantly lower than in controls on days 5, 7, and 14 after dosing; however, secretion of corticosterone induced by stimulation with exogenous ACTH was not altered by treatment with 2,3,7,8-TCDD. Based on these results, the authors concluded that 2,3,7,8-TCDD may interfere with secretion or synthesis of appropriate, bioactive ACTH from the anterior pituitary gland, which could compromise adrenal steroidogenesis.

The effects of 2,3,7,8-TCDD on thyroid function has been extensively studied. For example, a single gavage dose of 25 µg 2,3,7,8-TCDD/kg significantly decreased serum levels of T4 and increased serum levels of triiodothyronine (T3) in male hooded rats 9 days after dosing (Bastomsky 1977). The decrease in T4 appeared to be the result of an increased biliary excretion of T4-glucuronide, and this was attributed to induction of UDP-glucuronyltransferase (UDPGT) by 2,3,7,8-TCDD. UDPGT catalyzes glucuronidation of T4 and clearance. The increase in T3 was consistent with increased thyroid secretion from thyrotropin (TSH) stimulation. Administration of a single dose of 6.25–100 µg 2,3,7,8-TCDD/kg by gavage to adult male Sprague-Dawley rats produced a significant dose-related decrease in serum T4 levels (50% of control with the lowest dose) 7 days after dosing (Potter et al. 1986). Serum levels of T3 were elevated in a dose-related manner, whereas levels of TSH achieved a maximum increase with the lowest dose. Potter et al. (1986) also observed a small 2,3,7,8-TCDD-related increase in thyroid weight, but no consistent pattern of histological alterations. Hermansky et al. (1988) reported a 65% decrease in serum T4 levels in female Sprague-Dawley rats 6 days after administration of 3 doses of 40 µg 2,3,7,8-TCDD/kg; however, in this study the authors observed a 9% increase in serum T3. A dose-related decrease in serum total T4 was observed in female Long Evans rats 4 days after a single dose of 5.3–60 µg 2,3,7,8-TCDD/kg; statistical significance was achieved with a 12 µg/kg dose (Fan and Rozman 1995). Total serum T3 was not significantly altered. However, 90 days after single doses of 27–60 µg 2,3,7,8-TCDD/kg total serum T4 and T3 were elevated, which led the authors to suggest that 2,3,7,8-TCDD triggers adaptive responses which persist after most of the chemical has cleared the organism (Fan and Rozman 1995). In male mink,

relative thyroid gland weight was increased over a 4-week period after administration of a single dose of 7.5 µg 2,3,7,8-TCDD/kg, but a dose of 5 µg/kg was without effect (Hochstein et al. 1988). Hochstein et al. (1988) also reported a significant dose-related increase in relative adrenal gland weight over a 2.5–7.5 µg 2,3,7,8-TCDD/kg dose range. However, when the weights were expressed as a percentage of brain weight, only the increase in the adrenal gland at 7.5 µg/kg was significant. The concentrations of plasma cortisol and free and bound T3 and T4 were slightly reduced as a result of 2,3,7,8-TCDD treatment (2.5 µg/kg, only dose level tested), but the differences relative to controls were not significant.

Acute effects of 2,3,7,8-TCDD on thyroid function have been also reported in mice. In contrast with observations in rats, in which 2,3,7,8-TCDD appears to have independent effects on T4 and T3 levels, serum T4 and T3 levels were decreased in a dose-dependent fashion in male C57BL/6J mice 8 days after a single gavage dose of 0.03–235 µg 2,3,7,8-TCDD/kg (Weber et al. 1995). A similar effect was observed in male DBA/2J mice treated with a single dose of 1–3,295 µg/kg. In C57BL/6J mice, maximum depression of thyroid hormones (35% of controls) was achieved with a dose of 133 µg/kg. In male DBA/2J mice, maximum reductions in T3 and T4 levels (40 and 20% of controls, respectively) were attained with the highest dose level (Weber et al. 1995). It should be noted that the Weber et al. (1995) study did not include statistical analysis of the results.

A significant decrease in serum total T4 was observed in male Sprague-Dawley rats administered 2,3,7,8-TCDD by gavage for 13 weeks at doses equivalent to 0.8 µg/kg/day, the only dose level tested (Viluksela et al. 1994). Serum total T3 was not significantly altered and neither was the relative or absolute weight of the pituitary. Similar results on thyroid function were reported in female Sprague-Dawley rats administered 2,3,7,8-TCDD by gavage for 30 weeks at doses equivalent to 0.0001–0.125 µg/kg/day (Sewall et al. 1995). The dose-related decrease in serum T4 was statistically significant beginning at the 0.035 µg/kg/day dose level. Serum levels of T3 were not significantly altered by treatment. Sewall et al. (1995) also reported that serum levels of TSH were increased about 3-fold in the highest-dose group. Treatment with 2,3,7,8-TCDD also induced UDP-glucuronosyltransferase-1. Administration of 2,3,7,8-TCDD in the diet also affected thyroid function as demonstrated by Van Birgelen et al. (1995) who found a significant dose-related decrease in plasma total T4 in female Sprague-Dawley rats at dietary doses of $0.047 µg/kg/day for 13 weeks; plasma total T3 was not altered with 2,3,7,8-TCDD doses of up to 1 µg/kg/day. Li and Rozman (1995) examined the reversibility of the 2,3,7,8-TCDD-induced decrease in serum T4 in male Sprague-Dawley rats. The rats were gavaged once a week for 10 weeks with doses equivalent to approximately 0.003–1.6 µg 2,3,7,8-TCDD/kg and this was

followed by a 6-week recovery period. Serum T4 levels were significantly depressed with 2,3,7,8-TCDD doses of $0.03 µg/kg in a dose-dependent fashion and remained low during the recovery period. Based on these results, the authors suggested that the ED_{50} for this dose-response is close to a total cumulative dose of 1 µg/kg.

No significant non-neoplastic lesions were observed in the thyroid, parathyroid, adrenal, and pituitary gland from male and female Sprague-Dawley rats maintained for 2 years on a diet that supplied 0.001, 0.01, or 0.1 µg 2,3,7,8-TCDD/kg/day (Kociba et al. 1978a). Similar results were obtained in male and female Osborne-Mendel rats and in male $B6C3F_1$ mice administered up to approximately 0.071 µg 2,3,7,8-TCDD/kg/day by gavage for 104 weeks, and in female $B6C3F_1$ mice given up to 0.3 µg 2,3,7,8-TCDD/kg/day (NTP 1982b).

Information regarding other CDD congeners is limited. Administration of 1,2,3,4,6,7,8-HpCDD by gavage for 13 weeks to male Sprague-Dawley rats in doses equivalent to 24–110 µg/kg/day produced a dose-related decrease in serum total T4 (Viluksela et al. 1994). Doses of #4 µg/kg/day were without significant effect. Serum levels of total T3 were not significantly affected by treatment. A more recent study reported a 69% decrease in serum T4 levels in male Sprague-Dawley rats administered doses equivalent to 3.8 µg 1,2,3,7,8-PeCDD/kg/day or 15.4 µg 1,2,3,4,7,8-HxCDD/kg/day for 13 weeks (Viluksela et al. 1998b). After an additional 13-week CDD-free period, T4 levels returned to near control levels. In females administered doses of 2.6 µg/kg/day of the penta-CDD or 10.3 µg/kg/day of the hexa-CDD, T4 serum levels were 40% below control levels at the end of the dosing period and 62% below controls at the end of the additional 13-week period. Serum T3 levels were not significantly affected by treatment with either congener (Viluksela et al. 1998b).

In summary, CDDs were shown to alter endocrine parameters mostly in rodent studies. One of the better characterized effects was a decrease in serum T4, caused apparently by CDD-induced T4 metabolism and excretion. Alterations in T3 levels were less consistent. Results from additional studies suggested that 2,3,7,8-TCDD may interfere with secretion and synthesis of ACTH in the pituitary.

Dermal Effects. A number of changes in the skin have been observed in rodents and monkeys. In monkeys, skin lesions seen after a single oral dose or repeated dosing resemble the chloracne observed in humans. Distinctive changes in rhesus monkeys included swelling and inflamed eyelids, nail loss, and facial hair loss with acneform lesions following acute exposure to a single dose of 70 µg/kg (McConnell et

al. 1978a). Monkeys had hair loss due to squamous metaplasia and keratinization of the sebaceous glands and hair follicles, and periorbital edema following intermediate-duration exposure to 0.011 µg/kg/day of 2,3,7,8-TCDD in the diet or exposure to 0.1 µg/day, 3 days a week for 3 weeks, but not in those exposed to 0.02 µg/kg/day (Allen et al. 1977; McNulty 1984). Rough hair coats were described in Syrian hamsters exposed to a single dose of 1,000 µg/kg 2,3,7,8-TCDD, but not in those exposed to 600 µg/kg (Henck et al. 1981). Skin thickening was observed in A2G-hr/+ mice exposed to 75 µg/kg 2,3,7,8-TCDD (Greig 1984). Chronic exposure by gavage to 2,3,7,8-TCDD induced dermatitis in $B6C3F_1$ mice at 0.36 µg/kg/day (Della Porta et al. 1987) and amyloidosis in Swiss mice at 0.001 µg/kg/day (Toth et al. 1979). In the $B6C3F_1$ mice, dermatitis regressed after discontinuation of treatment (Della Porta et al. 1987). In contrast, no dermal effects were observed in Osborne-Mendel rats and in $B6C3F_1$ mice following chronic exposure to 0.71 µg/kg/day and 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively, by gavage for 104 weeks (NTP 1982b).

No dermal effects were found in Osborne-Mendel rats and $B6C3F_1$ mice gavaged with approximately 0.34 µg/kg/day and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, for 104 weeks (NCI/NTP 1980). However, male and female Sprague-Dawley rats treated with doses equivalent to 2.6–3.8 µg 1,2,3,7,8-PeCDD/kg/day or 10.3–15.4 µg 1,2,3,4,7,8-HxCDD/kg/day for 13 weeks exhibited occasional hair loss and sores in the ears, nose, neck, tail, and feet (Viluksela et al. 1998a). No effects were observed following chronic exposure of Osborne-Mendel rats and $B6C3F_1$ mice to 5×10^5 µg/kg/day and 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively, in the feed (NCI/NTP 1979a).

Ocular Effects. No ocular effects were observed in Osborne-Mendel rats and in $B6C3F_1$ mice following chronic exposure to 0.071 µg/kg/day and 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively, by gavage for 104 weeks (NTP 1982b). Also no ocular effects were found in Osborne-Mendel rats and $B6C3F_1$ mice gavaged with approximately 0.34 µg/kg/day and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, for 104 weeks (NCI/NTP 1980). Similarly, no effects were observed following chronic exposure of Osborne-Mendel rats and $B6C3F_1$ mice to 5×10^5 µg/kg/day and 1.3×10^6 µg/kg/day of 2,7-DCDD, respectively, in the feed (NCI/NTP 1979a).

Body Weight Effects. A characteristic effect of exposure to 2,3,7,8-TCDD in animals is the wasting syndrome. This is observed following exposure in all duration categories.

Weight loss or decreased weight gain were recorded in Sprague-Dawley rats following a single dose of 6.25 µg/kg (Moore et al. 1985), 10.6 µg/kg (Roth et al. 1988), 15 µg/kg (Seefeld and Peterson 1984), and 25 µg/kg 2,3,7,8-TCDD (Christian et al. 1986a), and in Fischer 344 rats following a single oral dose of 100 µg/kg (Kelling et al. 1985). Furthermore, about 40% weight loss was recorded in the range of LD_{50} values (164–340 µg/kg) for Fischer 344 rats from different breeding stations (Walden and Schiller 1985). None of the studies provided a NOAEL value. Acute exposure (10–14 days) to lower doses of 2,3,7,8-TCDD caused reduced weight gain in rats at 0.5 µg/kg/day, but not at 0.125 µg/kg/day (Giavini et al. 1983; Sparschu et al. 1971b).

Decreased body weight gain was observed in guinea pigs after a single dose of 6 µg/kg 2,3,7,8-TCDD in oil vehicle but not after 12 µg/kg in soil (Umbreit et al. 1985). A decreased weight gain was recorded in pregnant rabbits exposed during gestation to 0.25 µg/kg/day (Giavini et al. 1982) and in hamsters exposed to 1,000 µg/kg (Henck et al. 1981). ED_{50} values (doses causing a 50% decrease in a measurable parameter relative to the control value) for reduced body weight gain were calculated for 2,3,7,8-TCDD as 1.8 µg/kg for Hartley guinea pigs, 89 µg/kg for Sprague-Dawley rats, 890 µg/kg for C57BL/6 mice, and 1,000 µg/kg for Syrian hamsters (Hanberg et al. 1989). Single doses of $75 µg 2,3,7,8-TCDD/kg produced a slight reduction in body weight in male C57BL/6J mice 8 days after dosing (Weber et al. 1995); feed intake was not affected during this period. In the same study, it was found that body weights of male DBA/2J mice dosed with 1–3,295 µg 2,3,7,8-TCDD/kg were significantly reduced at $1,500 µg 2,3,7,8-TCDD/kg. It should be noted, however, that in mice, decreases in body weight resulting from 2,3,7,8-TCDD exposure do not become evident until 5–7 days after dosing (Shen et al. 1991), and that in C57BL/6J mice reduction of feed intake is insignificant during the first week after dosing (Kelling et al. 1985). Weight loss (28%) was also found in monkeys after a single dose of 70 µg/kg 2,3,7,8-TCDD (McConnell et al. 1978a).

Decreases in body weight gain or body weight loss have been consistently reported in animals following intermediate-duration exposures to 2,3,7,8-TCDD. A decreased weight gain was observed in Osborne-Mendel rats exposed intermittently for 13 weeks by gavage to 0.07 µg/kg/day (NTP 1982b) or in Sprague-Dawley rats treated with $0.2 µg/kg/day for 10–13 weeks (Li and Rozman 1995; Viluksela et al. 1994), in guinea pigs exposed to 0.005 µg/kg/day in the feed (DeCaprio et al. 1986), and in mice intermittently exposed to 20 µg/kg/day by gavage (Thigpen et al. 1975). A weight loss was recorded in rhesus monkeys after 0.1 µg/kg/day of 2,3,7,8-TCDD for 3 weeks of intermittent exposure (McNulty 1984). However, weight loss occurred with longer exposure of 9 months at 0.011 µg/kg/day (Allen et al. 1977). A recent study reported a 10% decrease in body weight gain in female Sprague-Dawley rats fed a diet that supplied

a daily dose of 0.047 µg 2,3,7,8-TCDD/kg for 13 weeks (Van Birgelen et al. 1995). At the highest exposure level (1 µg/kg/day) terminal body weights were reduced to 72% of controls; this group consumed 32% less food than controls.

In chronic-duration experiments with 2,3,7,8-TCDD, decreased body weight gain was reported in Sprague-Dawley rats exposed to 0.1 µg/kg/day (Kociba et al. 1978a) and 0.286 µg/kg/day (Van Miller et al. 1977) in the feed; Osborne Mendel rats exposed to approximately 0.0014 µg/kg/day by gavage for 104 weeks (NTP 1982b); and in $B6C3F_1$ mice exposed to 0.36 µg/kg/day by gavage for 52 weeks (Della Porta et al. 1987), but not in C57BL/6 mice gavaged once per week for 14–15 months with 0.03 µg 2,3,7,8-TCDD (Oughton et al. 1995).

Experiments with other congeners showed milder effects. Acute exposure during gestation caused a decreased maternal weight gain in Sprague-Dawley rats exposed to 10 µg/kg/day mixed HxCDD (Schwetz et al. 1973). Decreased weight gains were observed in rats and mice gavaged for intermediate-duration with 0.71 µg/kg/day and 0.18 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively (NCI/NTP 1980). Chronic-duration exposure induced decreased weight gain in Osborne Mendel rats exposed to 0.18 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD by gavage for 104 weeks (NCI/NTP 1980). In contrast, no effects on body weight were observed in mice exposed to 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD for 104 weeks (NCI/NTP 1980). Male Sprague-Dawley rats administered 1,2,3,4,6,7,8-HpCDD by gavage at dose levels equivalent to 73 and 110 µg/kg/day for 13 weeks exhibited a 5.1% and 19.3% reduction in body weight gain, respectively, at the end of the study period (Viluksela et al. 1994). No significant effect was observed with doses #24 µg/kg/day. Relative to controls, the body weight of male Sprague-Dawley rats administered doses equivalent to 3.8 µg 1,2,3,7,8-PeCDD/kg/day or 15.4 µg 1,2,3,4,7,8-HxCDD/kg/day for 13 weeks was reduced by 27% and 24%, respectively, at the end of the dosing period (Viluksela et al. 1998a). In females, doses equivalent to 2.6 µg 1,2,3,7,8-PeCDD/kg/day for 13 weeks resulted in an 18% reduction in body weight relative to controls, whereas doses of approximately 10.3 µg 1,2,3,4,7,8-HxCDD/kg/day for 13 weeks were without significant effect (Viluksela et al. 1998a).

No effect on the body weight of CD-1 mice was observed after 14 daily doses of OCDD at 1 µg/kg/day or 2,7-DCDD at 1,000 µg/kg/day (Courtney 1976). Chronic-duration exposure induced decreased weight gain in Osborne Mendel rats and in $B6C3F_1$ mice exposed to 2.5×10^5 µg/kg/day and 6.5×10^5 µg/kg/day of 2,7-DCDD, respectively, in the feed (NCI/NTP 1979a).

As summarized above, body weight effects were consistently observed in all species exposed to CDDs. Effects occurred after intermittent exposure by gavage and after exposure in a diet. In acute- and intermediate-duration exposure experiments, the wasting syndrome seemed to be the primary cause of death.

2.2.2.3 Immunological Effects

An effect of sublethal exposures (acute, intermediate-term, or chronic) to 2,3,7,8-TCDD common to all species studied is thymic atrophy. Depletion of lymphocytes results in suppression of T-cell immunity. The T-cell responses studied have included delayed hypersensitivity responses, rejection of skin allografts, and *in vitro* mutagen responses of lymphoid cells. T-cell immunotoxicity is probably the most sensitive end point. Effects on T-cells can occur at levels of exposure three orders of magnitude lower than the effects on thymus cellularity. B-lymphocytes are also affected by 2,3,7,8-TCDD, but higher exposure levels are necessary for suppression of humoral immunity. CDDs suppress resistance to different infectious agents by various mechanisms (see Section 2.4 for more detailed information).

Acute ED_{50} values for thymic atrophy following a single dose of 2,3,7,8-TCDD were calculated as 26 µg/kg in Sprague-Dawley rats, 0.8 µg/kg in Hartley guinea pigs, 280 µg/kg in C57BL/6 mice, and 48 µg/kg in Syrian hamsters (Hanberg et al. 1989). A significant dose-related reduction in absolute thymus weight was reported in young male Wistar rats administered single doses of $1 µg/kg 2,3,7,8-TCDD; this effect was paralleled by a significant decrease in thymic cellularity (De Heer et al. 1994b). Thymic atrophy was shown to be initiated in the thymus cortex on day 4 after a single dose of 25 µg/kg 2,3,7,8-TCDD (De Heer et al. 1994a). The initial lymphodepletion in the cortex was followed by a secondary depletion of medullary thymocytes on day 6, and on day 10, a preferential depletion of cortical thymocytes was no longer observed. Decreased thymus weight was reported in pregnant C57BL/6J mice exposed to 0.5 µg/kg/day 2,3,7,8-TCDD for 10 days (Silkworth et al. 1989b). Offspring of C57BL/6J mice similarly exposed to 1.5 µg/kg/day had severe thymic atrophy, cellular depletion and altered thymocyte antigen expression, and immune function (Holladay et al. 1991). In contrast, similar changes were observed in DBA/2J mice only after exposure to higher doses of 8 µg/kg/day. Furthermore, thymic atrophy was observed in rhesus monkeys after a single dose of 70 µg/kg (McConnell et al. 1978a) and in guinea pigs after a dose of 6 µg/kg (Umbreit et al. 1985).

Treatment of rats with daily doses of 0.72 µg 2,3,7,8-TCDD/kg/day by gavage for 14 days did not alter spontaneous NK-cell activity in the lung, but significantly suppressed influenza virus-augmented NK activity (Yang et al. 1994). A significantly higher virus titer was observed on days 2, 3, and 4 in whole lung homogenate from rats treated with a single dose of 10 µg/kg (Yang et al. 1994). Decreased resistance to infection, as evidenced by increased mortality, was observed in $B6C3F_1$ mice infected with *Streptococcus pneumoniae* and administered 1 µg/kg/day 2,3,7,8-TCDD for 14 days (White et al. 1986), and in $B6C3F_1$ mice infected with influenza A virus and administered a single gavage dose of 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD (Burleson et al. 1996). The Burleson et al. (1996) study identified a NOAEL of 0.005 µg/kg for this effect. Acute exposure to 2,3,7,8-TCDD reduced polymorphonuclear activity in $B6C3F_1$ mice at 5 µg/kg (no effect was seen in DBA/2N mice) (Ackermann et al. 1989). Suppressed antibody response to sheep erythrocytes (SRBC) was reported in $B6C3F_1$ mice that were given a single gavage dose of 1 µg/kg; no such effect was found after a single dose of 0.5 µg/kg (Holsapple et al. 1986a). However, suppression of the antibody response occurred after 14 daily doses of 0.1 µg/kg/day. In rats, a single dose of 20 µg 2,3,7,8-TCDD/kg administered 5 days before immunization significantly enhanced the primary antibody response to SRBC as judged by a significant increase in serum IgG levels 7 days after immunization (Fan et al. 1996). However, serum IgM levels were not significantly affected by doses of 2,3,7,8-TCDD of up to 40 µg/kg. Fan et al. (1996) also observed that cell-mediated immunity, tested with a delayed-type hypersensitivity (DTH) assay, exhibited a U-shaped response to treatment with 2,3,7,8-TCDD, as doses of 1–20 µg/kg increased the DTH response, whereas doses of 30–90 µg/kg decreased it, even below control levels.

Suppressed total serum complement activity was observed in female $B6C3F_1$ mice exposed to a single gavage dose of 14 µg/kg or 14 daily doses of 0.01 µg/kg/day (White et al. 1986). Serum levels of complement component C3 were also suppressed at doses of $0.5 µg/kg 2,3,7,8-TCDD (White et al. 1986). Subsequent studies by the same group showed that the 2,3,7,8-TCDD-induced reduction in serum C3 is not the result of a decrease in C3 production by hepatocytes but, at least in part, may be due to increased catabolism (Lin and White 1993). Single gavage doses of $2.5 µg 2,3,7,8-TCDD/kg suppressed cytotoxic T-lymphocyte (CTL) activity in mice challenged with a tumor allograft by a mechanism that did not involve elevation in plasma glucocorticoid levels (De Krey and Kerkvliet 1995). This was directly correlated with reduced numbers of splenic CTL effector cells (Kerkvliet et al. 1996). In these same animals, a suppression of the alloantibody response was correlated with a decreased expansion of the B-cell splenocyte population. This dose of 2,3,7,8-TCDD also initially induced interferon-γ, interleukin-2, and tumor necrosis factor production, but the normal increase of these in response to the tumor allograft was

not observed. Based on these and additional studies, the authors concluded that these effects are due to TCDD initially interfering with the activation of $CD4^+$ T cells and possibly T helper-B cell interactions. A recent study from the same group of investigators presented evidence that immune 2,3,7,8-TCDD-induced suppression in C57BL/6 mice is not caused by direct alterations in the production of immunomodulatory metabolites of arachidonic acid (Lawrence and Kerkvliet 1997). The above results indicate that immunological effects occur after moderate-to-low single doses or after repeated low doses that accumulate in the body, suggesting that the total dose of 2,3,7,8-TCDD is important. As shown in Figure 2-1, immunotoxicity was a very sensitive end point; the lowest LOAEL for immune effects is 0.01 µg/kg/day (Burleson et al. 1996; White et al. 1986). In the Burleson et al. (1996) study, decreased resistance to infection was observed in mice receiving a single gavage dose of 0.01 µg/kg, and no effects were observed at 0.005 µg/kg. Reduced serum complement levels were observed in mice exposed to 0.01 µg/kg/day for 14 days (White et al. 1986); no NOAEL was identified in this study. The NOAEL of 0.005 µg/kg/day identified in the Burleson et al. (1996) study was used to derive an acute oral MRL for 2,3,7,8-TCDD of 2×10^{-4} µg/kg/day as described in the footnote to Table 2-2, Section 2-5, and in Appendix A.

Several immunological effects were observed following intermediate-duration exposure to 2,3,7,8-TCDD. Decreased thymus weight after 2,3,7,8-TCDD exposure was observed in rats dosed by gavage with 0.71 µg/kg/day for 6 weeks (Vos et al. 1973), in the F_3 generation of rats receiving 0.01 µg/kg/day (Murray et al. 1979), and in guinea pigs receiving 0.005 µg/kg/day or 0.03 µg/kg/day (thymic atrophy) in the feed for 90 days (DeCaprio et al. 1986). A significant reduction in absolute and relative thymus weight was observed in male Sprague-Dawley rats administered 2,3,7,8-TCDD by gavage at doses equivalent to 0.8 µg/kg/day (only dose level tested) for 13 weeks (Viluksela et al. 1994). Spleen weight was not significantly altered. Similar results were reported in female Sprague-Dawley rats fed for 13 weeks a diet that supplied doses of $0.014 µg 2,3,7,8-TCDD/kg/day (Van Birgelen et al. 1995). Relative spleen weight was increased at $0.047 µg 2,3,7,8-TCDD/kg/day. Decreased cell-mediated immunity was found in mice and guinea pigs exposed by gavage to 0.71 µg/kg/day for 4 weeks and 0.03 µg/kg/day for 8 weeks, respectively (Vos et al. 1973). Guinea pigs seem to be especially sensitive to 2,3,7,8-TCDD toxicity; an intermediate-duration exposure to 0.001 µg/kg/day reduced the lymphocyte counts, and exposure to 0.03 µg/kg/day caused decreased humoral immunity and thymic atrophy (Vos et al. 1973). A recent study examined the effect of low-level dietary exposure to 2,3,7,8-TCDD to young adult male Leeds strain rats (Badesha et al. 1995). A 30-day exposure to approximately 0.1 µg/kg/day (or a total dose of approximately 3 µg/kg) resulted in an exposure duration-dependent reduction of *in vitro* lipopoly-saccharide-induced production of interleukin-1 in cultures of their splenic macrophages. A 180-day

exposure to approximately 0.017 µg/kg/day suppressed the production of interleukin-2 by either concanavalin A or phorbol ester/calcium ionophore stimulation, and reduced the lectin-induced proliferation of splenic T cells. The authors concluded that exposure to a low dietary dose of 2,3,7,8-TCDD suppresses the functions of several T-cell subsets. The highest NOAEL value for immunological effects (decreased thymus weight) was 0.0007 µg/kg/day 2,3,7,8-TCDD given to the most sensitive species, guinea pigs, in the diet (DeCaprio et al. 1986). The NOAEL value of 0.0007 µg/kg/day was used to derive an intermediate-duration oral MRL for 2,3,7,8-TCDD of 2×10^{-5} µg/kg/day as described in the footnote to Table 2-2, Section 2.5, and in Appendix A.

Increased mortality that was indicative of altered immunity was also observed in C57BL/6Jfh mice challenged with *Salmonella bern* following exposure to $1 µg/kg/day of 2,3,7,8-TCDD by gavage once a week for 4 weeks (Thigpen et al. 1975); no significant effects were observed at 0.5 µg/kg/day. In the same study, using the same experimental design, doses of up to 20 µg/kg/day of 2,3,7,8-TCDD had no significant effect on mortality in mice infected with *Herpesvirus suis* (Thigpen et al. 1975). Exposure to 0.5 µg/kg/day 2,3,7,8-TCDD once a week for 5–8 weeks caused suppression of humoral activity in C57BL/6 mice (Vecchi et al. 1983a). In addition, lymph node atrophy was reported in monkeys exposed to a lethal dose of 0.011 µg/kg/day in the feed for 9 months (Allen et al. 1971).

Administration of 2,3,7,8-TCDD at approximately 0.071 µg/kg/day to Osborne-Mendel rats or at about 0.3 µg/kg/day to B6C3F1 mice by gavage for 104 weeks produced no histological alterations in the spleen or thymus (NTP 1982b). Chronic exposure to 2,3,7,8-TCDD in food induced thymic atrophy in Sprague-Dawley rats at 0.1 µg/kg/day in a 2-year study (Kociba et al. 1978a) with the highest NOAEL of 0.01 µg/kg/day. Furthermore, rhesus monkeys exposed chronically to 0.002 µg/kg/day 2,3,7,8-TCDD in the feed exhibited degeneration of the bone marrow and lymphoid tissues (Hong et al. 1989). A recent study examined the effect of long-term exposure to 2,3,7,8-TCDD on various immune cell phenotypes of female C57 BL/6 mice (Oughton et al. 1995). The mice were administered 0.2 µg 2,3,7,8-TCDD/kg once per week for 14–15 months; this resulted in a cumulative dose of 12–13 µg/kg (approximately 0.03 µg/kg/day) and a concentration of 2,3,7,8-TCDD in adipose tissue of 1.27 ng/g abdominal fat. There were no significant 2,3,7,8-TCDD-related effects on thymus and spleen weight or in the cellularity of these tissues. Exposure to 2,3,7,8-TCDD induced subtle changes in thymic phenotypes which, according to the authors, were of questionable biological relevance given the age-related decrease in thymic cellularity observed. 2,3,7,8-TCDD did not alter the frequencies of the major leukocyte subpopulations, but significantly altered functionally discrete subpopulations within the T-cell compartment. The most notable

change was a decrease in the frequency of memory T helper cells, with a concomitant increase in the proportion of naive T helper cells. Oughton et al. (1995) also presented preliminary data suggesting that phenotypic changes in spleen cells correlated with similar changes in blood cells.

Other CDD congeners also appear to affect the immune system. Significant dose-related decreases in absolute and relative thymus weight were observed in male Sprague-Dawley rats administered doses equivalent to 4–110 µg/kg/day 1,2,3,4,6,7,8-HpCDD for 13 weeks by gavage (Viluksela et al. 1994). A dose level of 0.3 µg/kg/day was without significant effect. Treatment with 1,2,3,4,6,7,8-HpCDD had no significant effect on spleen weight. Suppressed antibody response was reported in $B6C3F_1$ mice after 2 weeks of exposure to 0.1 µg/kg/day of 2,7-DCDD, but not after exposure to 10 µg/kg/day of OCDD (Holsapple et al. 1986b). Depressed antibody response was found in C57BL/6 mice exposed to a single dose of 33 µg/kg/day 1,2,3,4,6,7,8-HpCDD (Kerkvliet and Brauner 1987). Suppressed serum complement activity was found in $B6C3F_1$ mice following 2 weeks of exposure to 1 µg/kg/day 1,2,3,6,7,8-HxCDD (White et al. 1986). Splenic hyperplasia was observed in Osborne-Mendel rats after exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD at 7.1 µg/kg/day, 1 day/week for 13 weeks (NCI/NTP 1980).

In conclusion, the immunological system was a sensitive target of CDD toxicity under experimental conditions in animals. Effects on all types of mediated immunity were seen at doses of 2,3,7,8-TCDD as low as 0.01 µg/kg. Doses of 2,3,7,8-TCDD that were well below the lethal dose affect humoral immunity. Thymic atrophy occurs as single or multiple doses approach those that may increase lethality. Neonates and young animals are much more sensitive than adults to most of the immunological responses.

The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category for each congener are recorded in Table 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

2.2.2.4 Neurological Effects

Limited information was obtained regarding neurological effects in animals. Decreased motor activity was observed in Sprague-Dawley rats after a single dose of 5 µg/kg of 2,3,7,8-TCDD that was not associated with mortality (Seefeld et al. 1984a) and after 14 daily doses of 2 µg/kg/day to pregnant females that were sacrificed on day 21 of gestation for developmental effects evaluation (Giavini et al. 1983). The NOAEL value was 0.01 µg/kg/day. Administration of 2,3,7,8-TCDD by gavage to male and female Osborne-

Mendel rats and male B6C3F1 mice at doses of up to 0.071 µg/kg/day for 104 weeks did not result in significant histological alterations in the brain, spinal cord, or sciatic nerve (NTP 1982b). The same was found for female B6C3F1 dosed with up to 0.3 µg/kg/day for the same time period (NTP 1982b).

Although motor effects have been described in rats dosed with 2,3,7,8-TCDD, in most studies, the neurological system was not specifically examined; therefore the issue of whether CDDs have a direct effect on the nervous system of animals has not been conclusively resolved.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

2.2.2.5 Reproductive Effects

A number of reproductive effects have been observed in animals orally exposed to 2,3,7,8-TCDD, including reduced fertility, pre- and post-implantation losses, decreases in gonad weights, decreased androgen levels, and altered estrus cycle and ovulation. Increased pre- and postimplantation losses were observed in CRCD rats exposed to 0.5 µg/kg/day for 2 weeks before mating (Giavini et al. 1983). Increased resorptions were found in Sprague-Dawley rats exposed to 0.125 µg/kg/day (Sparschu et al. 1971a), in CF-1 mice exposed to 1.0 µg/kg/day (Smith et al. 1976), and in NMRI mice exposed to 9 µg/kg/day (Neubert and Dillmann 1972) on gestation days (Gd) 6–15. In rabbits, increased postimplantation losses were recorded in a group exposed to 0.25 µg/kg/day, but not in those exposed to 0.1 µg/kg/day on Gd 6–15 (Giavini et al. 1982). Furthermore, increased abortions (10 of 12) were observed in monkeys after a single gavage dose of 1 µg/kg (McNulty 1984).

Reproductive toxicity has also been observed in non-pregnant female rats. Significant decreases in ovarian weight, ovulation rate, and the number of ova released have been observed in female Sprague-Dawley rats receiving a single gavage dose of $10 µg/kg (Li et al. 1995a, 1995b). Effects on hormone levels were also observed in the rats. Within 24 hours after dosing, significant increases in LH and follicle stimulating hormone levels were observed; prolactin levels were not altered (Li et al. 1995a). Following the administration of 17β-estradiol, LH and follicle stimulating hormone levels dropped below control levels.

2,3,7,8-TCDD is also a reproductive toxicant in males. Decreased seminal vesicle weight was reported in Sprague-Dawley rats after a single dose of 4.5 µg/kg, with decreased androgen levels detected only on day

6 postexposure (Moore et al. 1985). Inflammation of the epididymis with sperm granuloma formation was reported in Wistar rats exposed to 4 µg/kg/day for 7 days, and decreases in the weight of male reproductive organs together with reduced levels of serum testosterone and dihydrotestosterone (compared with the pair-fed controls) were seen in Sprague-Dawley rats after a single gavage dose of 12.5 µg/kg 2,3,7,8-TCDD (Khera and Ruddick 1973). An ED_{50} for altered regulation of LH levels was calculated as 10 µg/kg 2,3,7,8-TCDD in Sprague-Dawley male rats (Bookstaff et al. 1990a). No dominant lethality was reported when male Wistar rats were given 12 µg/kg/day 2,3,7,8-TCDD for 7 days before mating (Khera and Ruddick 1973).

In intermediate-duration studies with 2,3,7,8-TCDD, increased mortality was found in the offspring of Swiss Webster mice that were kept on a diet providing 0.35 µg/kg/day 2,3,7,8-TCDD for 4 weeks before mating, during gestation, and for 3 weeks of lactation (Thomas and Hinsdill 1979). Blocked estrous cycle was observed in female C57BL/6 mice exposed by gavage to 3 µg/kg/day, 3 days a week for 25 weeks (Umbreit et al. 1987), but no reproductive effects were seen in male mice exposed 1 day/week for 30 weeks to the same dose (Umbreit et al. 1988). However, reduced spermatogenesis was found in Sprague-Dawley rats exposed for 4 weeks to 3.4 µg/kg/day in the feed, but not in those similarly exposed to 0.286 µg/kg/day (Van Miller et al. 1977). Exposure of female rhesus monkeys to 0.1 µg/kg/day 3 days a week by gavage for 3 weeks caused abortions in 3 of the 4 monkeys; 1 of the 4 monkeys administered 0.02 µg/kg/day aborted (McNulty 1984). In a 3-generation study with 2,3,7,8-TCDD, significantly reduced fertility was observed among F_1- and F_2-generation rats exposed before mating to 0.01 µg/kg/day in the feed for 90 days, but not in those exposed to 0.001 µg/kg/day (Murray et al. 1979).

In chronic-duration studies, increased abortions and reduced reproduction rates were reported in monkeys exposed to 0.00064 µg/kg/day of 2,3,7,8-TCDD in the feed (Bowman et al. 1989b; Hong et al. 1989; Schantz et al. 1992). No reproductive effects were found at 0.00012 µg/kg/day. No changes were observed in the reproductive organs of Sprague-Dawley rats chronically exposed to 0.1 µg/kg/day in the feed (Kociba et al. 1978a), or Osborne-Mendel rats and $B6C3F_1$ mice exposed by gavage to approximately 0.0.71µg/kg/day and 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively (NTP 1982b).

Rier et al. (1993) found a dose-related increase in the incidence and severity of endometriosis in monkeys chronically exposed to 0.00012 or 0.00064 µg/kg/day of 2,3,7,8-TCDD in the diet. Surgical-induced endometriosis was enhanced by 2,3,7,8-TCDD exposure in rats and mice. In a surgically induced endometriosis model, significant increases in the diameter of the endometriotic site and an acceleration of

growth were observed in rats (Cummings et al. 1996) and mice (Cummings et al. 1996; Johnson et al. 1997), respectively. In this model, the animals received a gavage dose of 2,3,7,8-TCDD every 3 weeks (first dose was administered 3 weeks prior to surgical induction of endometriosis) for a total of five doses. Mice appear to be more sensitive than rats in terms of the magnitude of the effect on endometrial site diameter and adverse effect levels (endometriosis promotion was observed at 1, 3, and 10 µg/kg in mice [Cummings et al. 1996; Johnson et al. 1997] and at 10 µg/kg [Cummings et al. 1996]; no effects were observed in rats at 3 µg/kg). In contrast to these results, Foster et al. (1997) found that 2,3,7,8-TCDD exposure suppressed endometrial growth in mice. In their model, the mice were not pre-exposed to 2,3,7,8-TCDD prior to the induction of endometriosis. Foster et al. (1997) notes that pre-exposure to 2,3,7,8-TCDD results in endometriosis development due to immune suppression rather than an estrogen-responsive disease.

Acute-duration studies examining reproductive effects have been conducted with other congeners. Increased resorptions were found in Sprague-Dawley rats exposed to 10 µg/kg/day mixed HxCDD during gestation but not in those exposed to 1 µg/kg/day (Schwetz et al. 1973). No reproductive effects were found in rats exposed to 1×10^5 µg/kg/day 2,7-DCDD or 5×10^5 µg/kg/day OCDD during gestation. Similarly, no reproductive effects were found in rats exposed to 800 µg/kg/day 1,2,3,4-TCDD or 2,000 µg/kg/day 2-MCDD, 2,3-DCDD, or 2,7-DCDD on Gd 6–15 (Khera and Ruddick 1973).

The above data demonstrate that exposure to CDDs caused reproductive effects in animals. 2,3,7,8-TCDD was the most potent congener. The effects included increased pre- and postimplantation losses in females, morphological and functional changes in male and female reproductive organs, and hormonal imbalance in both sexes.

The highest NOAEL values and all reliable representative LOAEL values for reproductive effects in each species and duration category for each congener are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

2.2.2.6 Developmental Effects

A number of developmental effects have been observed in animals acutely exposed to 2,3,7,8-TCDD by the oral route. The types of effects observed in the offspring of animals exposed to 2,3,7,8-TCDD include structural malformations-cleft palate and kidney anomalies, functional alterations-damage to the immune

system and impaired development of the reproductive system, decreased growth, and fetal/newborn mortality.

Cleft palate and other skeletal anomalies have been observed in the offspring of CRCD rats exposed to 2 µg/kg/day for 2 weeks prior to conception (Giavini et al. 1983), in Long Evans rats exposed to 5 µg/kg on Gd 8 (Huuskonen et al. 1994), in rabbits exposed to 0.1 µg/kg/day during Gd 6–15 (Giavini et al. 1982), in C57BL/6N mice exposed to 12 µg/kg once on Gd 10 (Weber et al. 1985), in C57BL/6 mice exposed to 6 µg/kg once on Gd 10 or 12 (Abbott and Birnbaum 1989a), in C57BL/6J mice exposed once to 15 µg/kg on Gd 9 (Dasenbrock et al. 1992), in CD-1 mice exposed to 25 µg/kg/day during Gd 7–16 (Courtney 1976), in CF-1 mice exposed to 1 µg/kg/day on Gd 6–15 (Smith et al. 1976), in DBA2J mice exposed to 150 µg/kg on Gd 9 (Dasenbrock et al. 1992), and in NMRI mice exposed to 3 µg/kg/day during Gd 6–15 (Neubert and Dillmann 1972). The incidence of cleft palate was not significantly altered in Han/Wistar rats exposed to 1 or 10 µg/kg on Gd 8 (Huuskonen et al. 1994), in Long Evans rats exposed to 1 µg/kg on Gd 8 (Huuskonen et al. 1994), or in C57BL/6N mice exposed to 3 µg/kg/day on Gd 10–13 (Abbott et al. 1992).

Kidney anomalies, mainly hydronephrosis, were found in the offspring of CRCD rats exposed to 2 µg/kg/day for 2 weeks prior to conception (Giavini et al. 1983), in Han/Wistar rats exposed to 10 µg/kg on Gd 8 (Huuskonen et al. 1994), in C57BL/6N mice exposed to 12 µg/kg on Gd 10 (Abbott et al. 1987a, 1987b), in C57BL/6N mice exposed to 1 µg/kg on Gd 10 (Moore et al. 1973), in CD-1 mice exposed during Gd 7–16 to 25 µg/kg/day (Courtney 1976), in C57BL/6J and DBA/2J mice exposed to 0.5 µg/kg/day 2,3,7,8-TCDD on Gd 6–15 (Silkworth et al. 1989b), in C57BL/6N mice exposed postnatally through contaminated mothers' milk (Couture-Haws et al. 1991b), and in Golden Syrian hamsters exposed to 1.5 µg/g on Gd 7 or 9 (Olson and McGarrigle 1992). An increase in the severity of nephrosis was observed in 4–5-month-old Syrian hamsters receiving a single dose of 2 µg/kg *in utero* on Gd 11(Gray et al. 1995). No significant increases in the incidence of hydronephrosis or dilatation of renal pelvis were observed in Long Evans rats exposed to 1 or 5 µg/kg on Gd 8 (Huuskonen et al. 1994) or Han/Wistar rats exposed to 1 µg/kg on Gd 8 (Huuskonen et al. 1994).

The immune system effects include thymic atrophy and immunosuppression. Thymic atrophy was found in pups of Sprague-Dawley rats exposed to a single dose of 10 µg/kg 2,3,7,8-TCDD on lactation day 1 (Håkansson et al. 1987) and in Long Evans and Han/Wistar rats exposed to 5 or 10 µg/kg, respectively, on Gd 8 (Huuskonen et al. 1994). At lower doses, the thymic atrophy may be transitory; thymic atrophy was

observed on Gd 19 in the offspring of F344 rats exposed to 3.0 µg/kg on Gd 14 but not on Gd 22 (Gehrs et al. 1997a). Similarly, transient thymus atrophy was observed in offspring of BALB/cGa mice exposed to 10 µg/kg on Gd 14 (Fine et al. 1989). A dose-related decrease in relative thymus weights was seen in offspring of rats dosed at levels of 0.005–0.35 µg/kg 2,3,7,8-TCDD on Gd 16 (Madsen and Larsen 1989). Severe thymic atrophy and cellular depletion occurred in offspring of C57BL/6N mice exposed to 1.5 or 3 µg/kg/day on Gd 6–14 (Blaylock et al. 1992; Holladay et al. 1991). Thymus size was not affected in the offspring of Long Evans or Han/Wistar rats exposed to 1 µg/kg on Gd 8 (Huuskonen et al. 1994). Reversible suppression of cell-mediated immunity was reported in pups of Fischer 344 rats exposed to 2,3,7,8-TCDD through the dosing of dams on lactation day 0, 7, and 14 with 5 µg/kg/day (Faith and Moore 1977). Increased neutrophils were found in pups of $B6C3F_1$ mice exposed to 1 µg/kg/day 2,3,7,8-TCDD on Gd 14 and lactation days 1, 7, and 14 (Luster et al. 1980). Furthermore, increased lymphocytes and decreased erythrocytes and hematocrit were recorded in groups exposed to 5 µg/kg/day. Alterations in thymocyte phenotypes have also been observed following *in utero* and/or lactational exposure. A decrease in the percentage of $CD3^-/CD4^-CD8^-$, $CD3^+/CD4^-CD8^-$, and $CD3^+/CD4^+CD8^+$ thymocytes and an increase in $CD3^+/CD4^-CD8^+$ thymocytes were observed in the offspring of F344 rats exposed to 1.0 or 3.0 µg/kg on Gd 14 (Gehrs et al. 1997a). A decrease in $CD4^-/CD8^-$ thymocytes was observed following *in utero*, lactation only, or *in utero* and lactational exposure to 1.0 µg/kg (administered on Gd 14) (Gehrs et al. 1997b). *In utero* and lactational exposure also resulted in an increase in the percentage of $CD4^-/CD8^+$ lymphocytes; this was not observed in the *in utero* only or lactation only groups. Gehrs et al. (1997b) also found a suppression of the delayed hypersensitivity response to BSA in 5-month-old male offsprings receiving *in utero* and lactational exposure.

A number of studies have found impaired development of the reproductive system in male and female animals exposed to 2,3,7,8-TCDD during gestation. 2,3,7,8-TCDD affects androgen levels, secondary sex organs, spermatogenesis, fertility, and sexual behaviors. Effects have been observed in male and female offspring, although most of the studies have focused on males. Malformations of external genitalia (clefting, hypospadias, and vaginal thread), delayed vaginal opening (only significant in rats exposed on Gd 15; Gray and Ostby 1995), decreased number of ovarian follicles (only tested in Gd 15-exposed rats), and decreased fertility have been observed in female offspring of Holtzman and Long Evans rats exposed to a single dose of 1 µg/kg on Gd 8 or 15 (Gray and Ostby 1995; Flaws et al. 1997; Heimler et al. 1998). Gd 8 exposure also resulted in accelerated onset of constant estrus, shortened reproductive lifespan, and increased incidences of cystic hyperplasia of the endometrium. Malformations of the external genitalia were also observed in the offspring of Long Evans rats exposed to 0.20 or 0.80 µg/kg on Gd 15 but not at

0.05 µg/kg (Gray et al. 1997a). The fertility rate was not adversely affected in the offspring, but there was an increase in time to pregnancy in the 0.80 µg/kg group. In a cross-fostering experiment (Gray et al. 1997a), similar morphological reproductive alterations were observed following *in utero* exposure to 1.0 µg/kg (Gd 15) but not after lactation-only exposure. Chaffin et al. (1996) found significant decreases in serum estrogen levels in the female offspring of Holtzman rats receiving a single dose of 1 µg/kg on Gd 15. This study also found an increase in estrogen receptor mRNA in the hypothalamus, uterus, and ovary and a decrease in the pituitary; an increase and a decrease in estrogen receptor binding DNA were found in the uterus and hypothalamus, respectively. 2,3,7,8-TCDD exposure did not alter gonadotropin secretion; no alterations in serum FSH, LH, or androstenedione levels were observed on postnatal day 21 (Chaffin et al. 1997).

In male Holtzman rats exposed to 1 µg/kg on Gd 15, significant decreases in plasma testosterone were observed on Gd 18–21 (Mably et al. 1992a). Additionally, the normal surge in testosterone levels that occurs 2 hours after birth was delayed until 4 hours after birth and the amplitude of the surge was lower in 2,3,7,8-TCDD-exposed male offspring. Bjerke and Peterson (1994) observed significant decreases in plasma testosterone levels in Holtzman rats at age 63 days following exposure to 1 µg/kg on Gd 15. But studies by Mably et al. (1992a) and Gray et al. (1995) did not find significant alterations in plasma testosterone levels in pre- and post-pubescent rats; although Mably et al. (1992a) did report a tendency toward dose-related decreases in plasma testosterone and 5α-dihydrotestosterone levels in Holtzman rats at age 32, 49, 63, and 120 days following perinatal exposure to 0.064–1 µg/kg on Gd 15. Roman et al. (1995) found similar decreases at age 32 and 49 days, but at day 63 the testosterone levels were similar to controls. Most studies found large inter-animal variations in plasma testosterone levels; this coupled with small sample sizes may have been a contributing factor in the conflicting results that were found. Luteinizing hormone levels (primary hormone stimulating testosterone production) were decreased in the 32-day-old male offspring of dams receiving a dose of 1 µg/kg on Gd 15; no significant alterations in LH levels were observed in 49-, 63-, or 120-day-old rats (Mably et al. 1992a). Additional effects on androgenic status (androgen concentrations and androgen-dependent structures and functions) have been observed. Significant decreases in anogenital distance (corrected for differences in body size by dividing by crown-rump length) were observed in male Holtzman rats exposed to $0.16 µg/kg on Gd 15 (Mably et al. 1992a); however, Bjerke and Peterson (1994), Bjerke et al. (1994a), and Gray et al. (1995) did not find significant alterations in anogenital distance (also corrected for body size) in Holtzman and Long Evans rats exposed to 0.7 or 1 µg/kg on Gd 15. More consistent results were found for other measures of androgenic status. Significant alterations included a delay in testis descent (Bjerke et al. 1994a), delay in

preputial separation (external indicator of delayed puberty) (Bjerke et al. 1994a; Gray et al. 1995, 1997b), decreased ventral prostate weight (Bjerke and Peterson 1994; Mably et al. 1992a), and decreased seminal vesicle weight (Bjerke and Peterson 1994; Bjerke et al. 1994a; Mably et al. 1992a). The results of the Mably et al. (1992a) study suggest that the decrease in ventral prostate weight may be the most sensitive indicator of 2,3,7,8-TCDD-induced toxicity on androgen status. Decreases were observed in the rats exposed to $0.064 µg/kg on Gd 15; the other effects were observed in rats exposed to $0.16 µg/kg. Decreases in absolute testis weight and cauda epididymis weight were observed in juvenile (Mably et al. 1992c), pubertal (Mably et al. 1992c), postpubertal (Bjerke and Peterson 1994; Mably et al. 1992c), and sexually mature (Gray et al. 1995; Mably et al. 1992c) rats prenatally exposed to 2,3,7,8-TCDD on Gd 15. The lowest LOAEL for these effects was 0.064 µg/day (decreased testes weight), identified in the Mably et al. (1992c) study. Recent studies from the same group of investigators have focused on evaluating the potential role of the Ah receptor (see section 2.4.2 for a detailed discussion on the Ah receptor-mediated mechanism of action of CDDs) on the developmental alterations of the male reproductive tract (Roman and Peterson 1998; Roman et al. 1998a, 1998b). These studies are summarized in Section 2.5.

Significant decreases in daily sperm production (Bjerke and Peterson 1994; Mably et al. 1992c; Sommer et al. 1996), the amount of mature sperm stored in the cauda epididymis (Bjerke and Peterson 1994; Gray et al. 1995; Mably et al. 1992c), and the amount of sperm ejaculated (Gray et al. 1995, 1997b) were observed in gestationally exposed rats. These adverse effects on spermatogenesis occurred at doses of $0.05 µg/kg (Gray et al. 1997b). Sommer et al. (1996) suggest that observed decreases in cauda epididymal sperm number is likely due to a decrease in daily sperm production and an increase in sperm phagocytosis in the excurrent duct system. Sommer et al. (1996) and Wilker et al. (1996) did not find alterations in sperm epididymal transit time. Significant decreases in follicle stimulating hormone levels (necessary for the initiation of spermatogenesis) have been observed in 32-day-old male rats receiving a perinatal dose of 0.064, 0.40, or 1 µg/kg on Gd 15, but not in 49-, 63-, or 120-day-old rats (Mably et al. 1992c). In 70- and 120-day-old males exposed to #1 µg/kg and mated with unexposed females, no significant alterations in reproductive outcomes (fertility index, gestational index, survival index) were observed (Mably et al. 1992c); however, a non-significant decrease in fertility index was observed in the 0.4 and 1 µg/kg males. Gray et al. (1995) found a significantly decreased number of implants when males exposed to 1 µg/kg on Gd 15 were mated with unexposed females. Altered fertility was not observed in the male offspring of rats exposed to 2,3,7,8-TCDD on Gd 8 (Gray et al. 1995). Several studies have found a demasculinization of sexual behavior (prolonged intromission latency, increased number of intromissions prior to ejaculation) (Bjerke et al. 1994b; Mably et al. 1992b) and partial feminization of sexual behavior (increased intensity of

lordosis and lordosis quotient) in male offspring of rats dosed with 2,3,7,8-TCDD on Gd 15 (Bjerke and Peterson 1994; Bjerke et al. 1994b; Mably et al. 1992b). Mably et al. (1992b) identified 0.16 µg/kg on Gd 15 as the lowest LOAEL for demasculinized and feminized behaviors with a NOAEL of 0.064 µg/kg. A demasculinization and feminization of male rats has also been observed in 2,3,7,8-TCDD-exposed males. In perinatally exposed castrated rats, no significant alteration in plasma LH levels were observed following injection of estradiol benzoate. However, the response to progesterone administration in the rats receiving 0.40 or 1 µg/kg on Gd 15 was similar to that seen in unexposed ovariectomized females, and the plasma LH levels were significantly higher than in control males (Mably et al. 1992b). Impaired development of the reproductive system has also been observed in male Syrian hamsters exposed to 2 µg/kg on Gd 11 (Gray et al. 1995). Decreased epididymal sperm reserves, decreased testis and cauda epididymides weight, and delayed puberty were observed.

Alterations in mammary gland differentiation (less differentiation) were observed in 50-day-old offspring from rats treated by gavage with 1 µg 2,3,7,8-TCDD/kg on gestation day 15 (Brown et al. 1998). Specifically, treatment with 2,3,7,8-TCDD resulted in significantly more terminal end buds and fewer lobules II. However, no such effect was seen in 21-day-old rats. Prenatal treatment with 2,3,7,8-TCDD also resulted in an increased number of mammary adenocarcinomas in the offspring in response to dimethylbenz[a]anthracene (DMBA) relative to rats treated with DMBA alone. The authors speculated that the decreased differentiation may have rendered the gland more susceptible to mammary cancer.

Intestinal hemorrhage (Khera and Ruddick 1973; Sparschu et al. 1971a), subcutaneous edema, and hemorrhages in brain (Khera and Ruddick 1973) were observed in the offspring of Wistar rats treated with 0.125 or 0.25 µg/kg/day 2,3,7,8-TCDD during Gd 6–15, and gastrointestinal hemorrhage was observed in Han/Wistar rats exposed to 10 µg/kg on Gd 8 or 12 (Huuskonen et al. 1994). Decreases in mammary gland size due to inhibition of cell proliferation and gland development were observed in female Sprague-Dawley rats dosed with 2.5 µg/kg/day at ages 25, 27, 29, and 31 days (Brown and Lamartiniere 1995). Exposure to 0.10 µg/kg/day 2,3,7,8-TCDD during gestational days 10–16 resulted in significant decreases in T4 levels in female Sprague-Dawley rat pups. Thyroxine levels were not significantly altered in male rats or in females exposed to 0.025 µg/kg/day, and no alterations were observed in triiodothyronine or TSH values in males and females exposed to either dose (Seo et al. 1995). A decrease in core body temperature was observed in the offspring of Long Evans rats exposed to 1 µg/kg on Gd 15; no effect on metabolic rate or evaporative heat loss was observed (Gordon et al. 1995).

Decreases in fetal and newborn body weight were observed in Holtzman rats exposed to 0.7 or 1 µg/kg on Gd 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a). No body weight effects were observed in C57BL/6N mouse fetuses exposed to maternal doses of 3 µg/kg on Gd 10–13 (Abbott et al. 1992). Crown-rump length was also decreased in Holtzman rats exposed to 1 µg/kg on Gd 15 (Bjerke and Peterson 1994).

Several studies have reported increased mortality in the offspring of rats and monkeys exposed to 2,3,7,8-TCDD during gestation. Fetal/newborn deaths have occurred at doses which were either non-toxic or minimally toxic to the mothers. Increased newborn mortality was observed in Holtzman rat pups exposed to 0.7 or 1 µg/kg on Gd 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a); and decreased numbers of live fetuses, caused by increased resorption and fetal deaths, were observed in monkeys after a single exposure to 1 µg/kg on Gd 25, 30, 35, or 40 (McNulty 1984) and in Long Evans or Han/Wistar rats exposed to 5 or 10 µg/kg, respectively, on Gd 8 (Huuskonen et al. 1994). After exposure of mouse dams to 12.5 µg/kg/day 2,3,7,8-TCDD on Gd 14–17, 75% lethality was observed in the pups (Nau et al. 1986).

In intermediate-duration exposure experiments, decreased neonatal survival was found in the F_1 and F_2 generations of Sprague-Dawley rats exposed via the feed to 0.01 µg/kg/day, but not to 0.001 µg/kg/day, of 2,3,7,8-TCDD in a 3-generation study (Murray et al. 1979). Thymic atrophy was found in offspring of Swiss Webster mice that were kept on a diet providing 0.35 µg/kg/day 2,3,7,8-TCDD for 4 weeks before mating, during gestation, and for 3 weeks of lactation (Thomas and Hinsdill 1979). No developmental effects were found in the offspring of C57BL/6 male mice treated with 3 µg/kg/day of 2,3,7,8-TCDD by gavage (in oil or soil vehicle) for 30 weeks (Umbreit et al. 1988). No fetal abnormalities were found in the 3 fetuses of rhesus monkeys administered 0.02 µg/kg/day 2,3,7,8-TCDD 3 days a week for 3 weeks (McNulty 1984). At the higher dosages (0.1 and 0.6 µg/kg/day) only 1 fetus (from the 0.1 µg/kg/day group) was not aborted.

Developmental effects of 2,3,7,8-TCDD after chronic exposure were studied in rhesus monkeys. Decreased offspring survival was found when mothers were exposed continuously during pregnancy to 6.4×10^{-4} µg/kg/day in the feed (Bowman et al. 1989b). In addition, alterations in peer-group behavior (Bowman et al. 1989b; Schantz et al. 1992) and cognitive deficits were observed in the offspring of rhesus monkeys exposed to 1.2×10^{-4} µg/kg/day in the diet for 7 months prior to mating and during mating and lactation (16 months total duration). Significant alterations were observed in play behavior, displacement, and self directed behavior. Exposed monkeys tended to initiate more rough-tumble play bouts and retreated

less from play bouts than controls, were less often displaced from preferred positions in the playroom than the controls, and engaged in more self-directed behavior than controls. Cognitive function was altered as evidenced by impaired-reversal-learning performance in the absence of impaired delayed-spatial-alterations performance (Bowman et al. 1989b; Schantz and Bowman 1989); no NOAEL was identified for these effects. Schantz et al. (1986) also found increased and prolonged maternal care of these infants. The LOAEL of 1.2×10^{-4} µg/kg/day identified for neurobehavioral effects identified in the Schantz et al. (1992) study was used to derive a chronic oral MRL of 1×10^{-6} µg/kg/day, as described in the footnote to Table 2-2, Section 2.5, and in Appendix A.

Other CDD congeners have also been found to induce developmental toxicity. Rat pups exposed *in utero* to 2,000 µg/kg/day 2,7-DCDD had edematous separation of the cardiac myofibrils (Khera and Ruddick 1973). Schwetz et al. (1973) found no developmental effects in fetuses of rats exposed to 100,000 µg/kg/day 2,7-DCDD during gestation, but histological examinations of soft tissues were not performed. Decreased thymic weight was found in the offspring of rats exposed once on Gd 16 to 0.125 µg/kg 1,2,3,7,8-PCDD (Madsen and Larsen 1989). Subcutaneous edema was found in the offspring of Sprague-Dawley rats exposed to 1 µg/kg/day of mixed HxCDD during Gd 6–15 (Schwetz et al. 1973). Furthermore, decreased fetal body weight, reduced crown-rump length, delayed ossification, and dilated renal pelvis were observed at 10 µg/kg/day, and an increased incidence of cleft palate was found at 100 µg/kg/day. The NOAEL for the mixture of HxCDD isomers was 0.1 µg/kg/day. Subcutaneous edema was also reported in fetuses of rats exposed to 5×10^{5} µg/kg/day of OCDD during Gd 6–15; no effects were found in the 1×10^{5} µg/kg/day OCDD-exposure group (Schwetz et al. 1973) or in mice exposed to 20 µg/kg/day of OCDD during Gd 7–16 (Courtney 1976). In contrast to most experiments with 2,3,7,8-TCDD, the 1,2,3,4-TCDD isomer did not induce developmental effects in the offspring of Wistar rats treated on Gd 6–15 with 800 µg/kg/day (Khera and Ruddick 1973) or CD-1 mice exposed to 1,000 µg/kg/day during gestation (Courtney 1976). No developmental effects were seen in the offspring of Wistar rats exposed to 2,000 µg/kg/day 2,3-DCDD or 2-MCDD on Gd 6–15 (Khera and Ruddick 1973).

In conclusion, studies in rodents and monkeys demonstrated that oral exposure to CDDs induced developmental effects with congeners primarily having chlorine atoms at the 2, 3, 7, and 8 positions. Following CDD exposure of dams, the primary effects observed in the offspring included cleft palates, hydronephrosis, impaired development of the reproductive system, immunotoxicity, and death. Effects were observed in offspring from dams exposed before mating and/or during gestation; transfer of CDDs via maternal milk also resulted in adverse developmental effects. Mice appear to be particularly sensitive to

the induction of cleft palate; this alteration also occurred in rats, but at dose levels that were maternally toxic. Alterations to the immune system from offspring (mostly rats and mice) included thymic atrophy, alterations in cell-mediated immunity, and changes in lymphocyte surface cell markers. The development of the reproductive systems of male and female rats was also affected by parental exposure to CDDs. Chronic exposure of monkeys starting before mating and continuing throughout gestation and lactation resulted in neurobehavioral alterations in the infants; this effect was used to derive a chronic oral MRL.

The highest NOAEL values and all reliable representative LOAEL values for developmental effects in each species and duration category for each congener are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

2.2.2.7 Genotoxic Effects

Mostly negative results were obtained in animal studies following oral exposure to 2,3,7,8-TCDD. Cytogenetic analysis of the bone marrow did not reveal any increase in chromosomal aberrations in CD-COBS rats exposed to 1 µg/kg 2,3,7,8-TCDD by gavage once a week for 45 weeks (Loprieno et al. 1982), but an increased incidence was reported in Osborne-Mendel rats exposed to 4 µg/kg twice a week for 13 weeks (Green et al. 1977). However, chromosomal aberrations were not increased in peripheral lymphocytes of monkeys exposed to 0.001 µg/kg/day in the feed for 4 years (Lim et al. 1987). Furthermore, 7 daily doses of 12 µg/kg did not induce dominant lethality in Wistar rats (Khera and Ruddick 1973). In addition, an intermediate-duration exposure to 1 µg/kg/week of 2,3,7,8-TCDD or 1,2,3,7,8-PCDD for up to 6 months did not enhance the formation of deoxyribonucleic acid (DNA) adducts in rat hepatocytes (Randerath et al. 1989). In conclusion, CDDs were not genotoxic in most animal studies. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

The carcinogenicity of CDDs has been demonstrated in several experiments in animals. Chronic exposure of male Osborne-Mendel rats to approximately 0.0071 µg 2,3,7,8-TCDD/kg/day by gavage significantly increased the incidence of thyroid follicular cell adenoma; in females, doses of approximately 0.071 µg/kg/day increased the incidence of neoplastic nodules in the liver and of hepatocellular carcinoma (NTP 1982b). Exposure to 0.00014 µg/kg/day 2,3,7,8-TCDD in the feed resulted in an increase in the number of tumor bearing male Sprague Dawley rats (5/6 versus 0/4 in control) (Van Miller et al. 1977).

The types of neoplasms found were ear duct carcinoma, lymphocytic leukemia, kidney adenocarcinoma, peritoneal malignant histiocytoma, skin angiosarcoma, and Leydig cell adenoma. Each tumor-bearing rat had different tumor types, and one rat had 2 types of tumors. The high mortality in the control group, inadequately reported results, and small group sizes (10/group) limit the interpretation of these results. Exposure to 0.1 µg/kg/day in the feed induced hepatocellular carcinoma, squamous cell carcinoma of lungs, and hard palate and tongue in Sprague-Dawley rats (Kociba et al. 1978a). A significant increase in hepatocellular hyperplastic nodules was observed in the female rats exposed to 0.01 or 0.1 µg/kg/day. Females were more affected by 2,3,7,8-TCDD exposure than males. 2,3,7,8-TCDD was also carcinogenic in mice exposed chronically by gavage. Hepatomas and hepatocellular carcinomas were induced in Swiss mice exposed to 0.1 µg/kg/day for 1 year (Toth et al. 1979). Increased incidence of hepatocellular carcinomas was observed in male B6C3F1 mice administered 2,3,7,8-TCDD at approximately 0.071 µg/kg/day by gavage for 104 weeks (NTP 1982b); females exhibited an increase in thyroid follicular cell adenomas and in histiocytic lymphoma at a dose of approximately 0.3 µg/kg/day (NTP 1982b). Hepatocellular carcinomas (males and females) and adenomas (females) were found in $B6C3F_1$ mice exposed to 0.36 µg/kg/day given by gavage for 1 year (Della Porta et al. 1987).

Experiments with other congeners showed that chronic exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD by gavage induced hepatocellular carcinoma, adenoma, and neoplastic nodules at approximately 0.34 µg/kg/day in female Osborne-Mendel rats and at 0.71 µg/kg/week in $B6C3F_1$ male mice (NCI/NTP 1980). Therefore, HxCDD is approximately 1/20 as potent a liver carcinogen as 2,3,7,8-TCDD. Furthermore, chronic exposure to 6.5×10^5 µg/kg/day of 2,7-DCDD in the feed caused leukemias, lymphomas, hemangiosarcomas, hemangiomas, and dose-related increased incidences of hepatocellular adenomas and carcinomas in male $B6C3F_1$ mice (NCI/NTP 1979a). In contrast, no cancer effects were observed following chronic exposure of Osborne-Mendel rats to 5×10^5 µg/kg/day of 2,7-DCDD (NCI/NTP 1979a) in the feed.

In conclusion, the tested congeners (2,3,7,8-TCDD, mixed HxCDDs) were carcinogenic in rodents. 2,7-DCDD was carcinogenic in mice, but not in rats that received a lower dose.

The cancer effect levels (CELs) for each species and duration category for each congener are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

Information regarding mortality following dermal exposure to CDDs in animals is limited. For 2,3,7,8-TCDD, a dermal LD_{50} value in rabbits was calculated as 275 µg/kg (Schwetz et al. 1973). Deaths occurred within 12–22 days, but the cause of death was not specifically indicated. Decreased survival was observed in Swiss Webster mice exposed 3 days a week to 2,3,7,8-TCDD at 0.05 µg for 13 weeks and 0.001 µg for chronic duration (NTP 1982a). In the subchronic study (NTP 1982a), male mice exhibited a higher mortality rate than females; lethal doses in males caused marked effects in lymphoid and hematopoietic tissues as well as on the liver and lung. The cause of death in the chronic study (NTP 1982a) was not specified. No increase in lethality was reported in HRS/J hairless mice dermally exposed to 0.0025 µg, 2 days a week, for 20 weeks (Hebert et al. 1990).

The LD_{50} value for rabbits and LOAEL values in mice for increased mortality for the intermediate- and chronic-duration categories are recorded in Tables 2-4 and 2-5.

2.2.3.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category for each congener are recorded in Table 2-4 and 2-5.

Respiratory Effects. Bronchiolar adenomatoid changes were found in Swiss Webster mice exposed 3 days a week to 0.05 µg 2,3,7,8-TCDD for 13 weeks, but no respiratory effects were observed in mice exposed 3 days per week to 0.01 µg for a chronic exposure period (NTP 1982a).

Cardiovascular Effects. Information regarding cardiovascular effects in animals after dermal exposure to CDDs is limited. Chronic dermal exposure of Swiss Webster mice to 2,3,7,8-TCDD at 0.005 µg, 3 days per week, did not induce any cardiovascular changes observable under histopathological examination (NTP 1982a).

Table 2-4. Levels of Significant Exposure to 2,3,7,8-TCDD - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
ACUTE EXPOSURE						
Death						
Rabbit (NS)	once				275 µg/kg (LD_{50})	Schwetz et al. 1973b
Systemic						
Mouse (HRS/J)	2 wk 3 d/wk 1x/d	Dermal		0.01 µg F (hyperkeratosis, involution of sebaceaus glands)		Puhvel and Sakamoto 1988
Rabbit (NS)	once	Dermal		2000 µg (transient inflammation of conjunctiva)		Schwetz et al. 1973b
INTERMEDIATE EXPOSURE						
Death						
Mouse (Swiss-Webster)	13 wk 3 d/wk				0.05 µg (10% died in both sexes)	NTP 1982a
Systemic						
Mouse (CD-1)	30 wk 2 d/wk	Dermal		0.1 µg F (acne-like lesion)		Berry et al. 1978; 1979

Table 2-4. Levels of Significant Exposure to 2,3,7,8-TCDD - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Mouse (HRS/J hairless)	20 wk 2 d/wk	Hepatic		0.0025 µg F	(increased relative liver weight)	Hebert et al. 1990
		Bd Wt		0.01 µg F	(16% decreased body weight gain)	
Mouse (Swiss-Webster)	13 wk 3 d/wk	Resp	0.01 µg	0.05 µg	(bronchiolar adenomatoid changes with hyperplasia)	NTP 1982a
		Hepatic		0.005 µg	(fatty degeneration)	
Mouse (HRS/J, Skh:HR-1)	4 wk 3 d/wk 1x/d	Hepatic		0.1 µg F	(increased microsomal enzyme-activity)	Puhvel et al. 1982
		Dermal		0.1 µg F	(hyperkeratosis absence of sebaceous glands)	

Table 2-4. Levels of Significant Exposure to 2,3,7,8-TCDD - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL			Reference
				Less Serious		Serious	
Immunological/Lymphoreticular							
Mouse (HRS/J)	20 wk 2 d/wk		0.005 µg F	0.01 µg F	(decreased thymus/ body weight ratio in non-initiated mice)		Herbert et al. 1990
Cancer							
Mouse (HRS/J hairless)	20 wk 2 d/wk					0.0025 µg F (increased number of skin squamous cell papilloma and hyperproliferative nodules)	Herbert et al. 1990
Mouse (HRS/J hairless)	20 wk 2 d/wk					0.00375 µg (skin papilloma following initiation)	Poland et al. 1982
CHRONIC EXPOSURE							
Death							
Mouse (Swiss-Webster)	99-104 wk 3 d/wk					0.001 µg (decreased survival)	NTP 1982a

Table 2-4. Levels of Significant Exposure to 2,3,7,8-TCDD - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Systemic						
Mouse (Swiss-Webster)	99-104 wk 5 d/wk	Resp	0.005 µg			NTP 1982a
		Cardio	0.005 µg			
		Gastro	0.005 µg			
		Hemato	0.005 µg			
		Hepatic	0.005 µg			
		Renal	0.005 µg			
		Dermal	0.005 µg			
		Bd Wt	0.005 µg			
Reproductive						
Mouse (Swiss-Webster)	99-104 wk 3 d/wk		0.005 µg			NTP 1982a

Table 2-4. Levels of Significant Exposure to 2,3,7,8-TCDD - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL			Reference
				Less Serious	Serious		
Cancer							
Mouse (Swiss-Webster)	99-104 wk 3 d/wk				0.005 µg	(CEL: fibrosarcoma without initiation)	NTP 1982a

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s) x = times.

Table 2-5. Levels of Significant Exposure to Dioxins (non-2,3,7,8-TCDD) - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (ug)	LOAEL		Reference Chemical Form
				Less Serious (ug)	Serious (ug)	
ACUTE EXPOSURE						
Systemic						
Rabbit (NS)	once	Dermal		2000 (transient inflammation of conjunctiva)		Schwetz et al. HCDD5
Rabbit (NS)	once	Dermal		(transient inflammation of conjunctiva)		Schwetz et al. OCDD
Rabbit (NS)	once	Dermal		(transient inflammation of conjunctiva)		Schwetz et al. 1973b DCDD1

DCDD1 = 2,7-dichlorodibenzo-p-dioxin; HCDD5 = unspecified mixture of hexachlorodibenzo-p-dioxins; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; NS = not specified; OCDD = octachlorodibenzo-p-dioxin

Gastrointestinal Effects. Information regarding gastrointestinal effects in animals after dermal exposure to CDDs is limited. No histopathological changes were observed in the gastrointestinal tract of Swiss Webster mice chronically exposed to 0.005 µg 2,3,7,8-TCDD 3 days per week (NTP 1982a).

Hematological Effects. Hematological examination of Swiss Webster mice chronically exposed to 0.005 µg 2,3,7,8-TCDD 3 days per week did not reveal any differences between exposed and control groups (NTP 1982a).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in animals after dermal exposure to CDDs.

Hepatic Effects. Hepatic effects have been observed in animals after dermal exposure to 2,3,7,8-TCDD. Necrosis, peripheral fibrosis, and bile duct proliferation were observed in rabbits acutely exposed to 2,3,7,8-TCDD on the ear surface (Kimbrough et al. 1977). Increased liver/body weight ratio and hepatocellular hypertrophy were seen in HRS/J hairless mice topically exposed to 0.0025 µg 2,3,7,8-TCDD twice a week for 20 weeks (Hebert et al. 1990). Fatty degeneration and hepatocellular necrosis were observed in the livers of Swiss Webster mice exposed to 0.005 µg 2,3,7,8-TCDD 3 days a week for 13 weeks (NTP 1982a). No hepatic effects were found in mice chronically exposed to 0.005 µg/day 2,3,7,8-TCDD (NTP 1982a). The data indicated that 2,3,7,8-TCDD induced hepatotoxic effects similar to those observed after oral exposure.

Renal Effects. Information regarding renal effects in animals after dermal exposure to 2,3,7,8-TCDD is limited. No histopathological changes were found in Swiss Webster mice exposed to 0.005 µg 2,3,7,8-TCDD 3 days per week for 99–104 weeks (NTP 1982a).

Dermal Effects. Dermal effects of several CDD congeners have been studied in animals. Acute dermal exposure to 0.01 µg (newborn) and 0.1 µg 2,3,7,8-TCDD (adult) per animal caused hyperkeratosis and epidermal hyperplasia in hairless HRS/J mice (Puhvel and Sakamoto 1988). An involution of sebaceous glands was found in both (haired and hairless) strains. Similar results were found following intermediate-duration exposure (Puhvel et al. 1982). Furthermore, acne-like lesions in the ears were found in CD-1 mice following exposure to 0.1 µg 2,3,7,8-TCDD applied on the pre-shaved back 2 days a week for 30 weeks (Berry et al. 1978, 1979). In contrast, no dermal effects were observed in Swiss Webster mice exposed to 0.005 µg 2,3,7,8-TCDD/application, 3 days a week for up to 104 weeks (NTP 1982a).

Ocular Effects. A single application of 2,000 µg 2,7-DCDD, 2,3,7,8-TCDD, mixed HxCDD, or OCDD into the conjunctival sac of rabbits caused transient pain and conjunctival inflammation (Schwetz et al. 1973). Delayed conjunctival chemosis was observed with 2,3,7,8-TCDD. None of the CDDs caused corneal injury or iritis.

Body Weight Effects. In animal studies, decreased body weight was observed in HRS/J and Skjh:HR-1 mice following intermediate-duration dermal exposure to 0.1 µg 2,3,7,8-TCDD (Puhvel et al. 1982) and in Swiss Webster mice following chronic exposure to 0.005 µg 2,3,7,8-TCDD 3 days per week (NTP 1982a).

2.2.2.3 Immunological Effects

The only information regarding immunological effects in animals after dermal exposure to CDDs was obtained from an intermediate-duration study in HRS/J mice (Hebert et al. 1990). Mice dermally exposed to 0.01 µg 2,3,7,8-TCDD 2 days per week for 20 weeks had decreased thymus/body weight ratio. No effects were observed at 0.005 µg.

The NOAEL and LOAEL values for immunological effects in mice after intermediate-duration exposure are recorded in Table 2-4.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in animals after dermal exposure to CDDs.

2.2.3.5 Reproductive Effects

Data regarding reproductive effects following dermal exposure in animals are scarce. No treatment-related changes were observed in the reproductive system of Swiss Webster mice after chronic exposure to 0.005 µg 2,3,7,8-TCDD per application (NTP 1982a).

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in animals after dermal exposure to CDDs.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in animals after dermal exposure to CDDs. Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

Acute- and intermediate-duration studies in animals investigated the interactions of 2,3,7,8-TCDD with known carcinogens. A single dermal pretreatment of CD-1 Charles River mice with 0.01 µg 2,3,7,8-TCDD inhibited the development of skin papillomas otherwise initiated by 1,3-dimethylbenz(*o*)anthracene (DMBA) (Berry et al. 1979). In intermediate-duration experiments, 2,3,7,8-TCDD did not promote skin tumors initiated by DMBA (Berry et al. 1978, 1979). In contrast, the promoting ability of 2,3,7,8-TCDD at 0.0025 µg/day (and higher), 2 days a week, for 20 weeks, was reported in HRS/J hairless mice following the initiation with N-methyl-N-nitro-N-nitrosoguanidine in intermediate-duration experiments (Hebert et al. 1990; Poland et al. 1982). The effect was not observed in mice heterozygous for the hairless trait (Poland et al. 1982). In a chronic study, significantly increased incidence of fibrosarcoma of the integumentary system was found in Swiss Webster female mice following dermal exposure to 2,3,7,8-TCDD at 0.005 µg, 3 days a week for 2 years (NTP 1982a). The cancer effect level (CEL) from this study is shown in Table 2-4.

2.3 TOXICOKINETICS

Data regarding toxicokinetics of CDDs in humans are limited to information derived from exposures that occurred after industrial accidents, exposures of Vietnam veterans, and ingestion of 2,3,7,8-TCDD by a volunteer. Humans can absorb CDDs by the inhalation, oral, and dermal routes of exposure. CDDs, when administered orally, are well absorbed by experimental animals, but they are absorbed less efficiently when administered by the dermal route. Limited data in rats showed that transpulmonary absorption of 2,3,7,8-TCDD may be at least as efficient as oral absorption. In a human volunteer, >86% of the administered single oral dose appeared to have been absorbed. In general, absorption is vehicle-dependent and congener-specific. Passage across the intestinal wall is predominantly limited by molecular size and solubility. These parameters are most significant for hepta- and octachlorinated congeners, which exhibit decreased absorption in mammals. The predominant CDD carriers in human plasma are serum lipids and

lipoproteins, but chlorine substitution plays a role in the distribution in these fractions. For most mammalian species, the liver and adipose tissue are the major storage sites of CDDs; in some species, skin and adrenals also can act as primary deposition sites. 2,3,7,8-Substituted CDDs are the predominant congeners retained in tissues and body fluids. Tissue deposition is congener-specific and depends on the dose, the route of administration, and age. CDDs are very slowly metabolized by the microsomal monooxygenase system to polar metabolites that can undergo conjugation with glucuronic acid and glutathione. The major routes of excretion of CDDs are the bile and the feces; smaller amounts are excreted via the urine. In mammalian species, lactation is an effective way of eliminating CDDs from the liver and other extrahepatic tissues. Physiologically based pharmacokinetic (PBPK) models have been developed to describe disposition of 2,3,7,8-TCDD in humans and animals. Some of these models included parameters to describe complex interactions of 2,3,7,8-TCDD with cellular proteins that lead to specific biological responses.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No quantitative data were located regarding absorption of CDDs in humans following inhalation exposure. However, based on data from studies with structurally related chemicals it is reasonable to assume that CDDs are absorbed by this route. Furthermore, data on levels of CDDs in blood from populations with above-background exposures (occupational, accidental) also suggest that transpulmonary absorption occurs in humans; see Section 2.1 for more information.

Systemic effects (hepatic aryl hydrocarbon hydroxylase [AHH] and cytochrome P-450 induction, hepatic histological alterations) were observed in rats following a single intratracheal instillation of 2,3,7,8-TCDD in a corn oil vehicle or as a laboratory-prepared contaminant of gallium oxide particles (Nessel et al. 1990). In a subsequent study, the same group of investigators (Nessel et al. 1992) using a similar protocol found that the relative pulmonary bioavailability of 2,3,7,8-TCDD on respirable soil particles was 100% as compared to the gallium oxide vehicle. One and 7 days post-treatment, 13.9 and 11.9% of the administered dose were detected in the liver, respectively, and this was similar to the percentage found after instillation of contaminated gallium oxide particles. Twenty-eight days after treatment, 5.2% of the administered dose was detected in the liver from soil-treated rats and 2.9% in liver from gallium oxide-treated rats suggesting that redistribution and retention of 2,3,7,8-TCDD differed in the two treatment groups. Recently, Diliberto

et al. (1996) reported that 3 days after intratracheal application of a single dose of 0.32 µg 2,3,7,8-TCDD/kg to male Fischer 344 rats, 95% of the applied dose was absorbed, suggesting that inhalation can be an effective route of exposure. The extent of inhalation absorption was higher than when the same dose was administered orally (88%) or dermally (40%). The available data suggest that inhaled CDDs will be absorbed. However, the degree of absorption and the rate will depend on the media on which the CDDs are adsorbed and the degree of chlorination.

2.3.1.2 Oral Exposure

The absorption of 2,3,7,8-TCDD was estimated to be >87% in a human volunteer following ingestion of a single radioactively labeled dose of 0.00114 µg 2,3,7,8-TCDD/kg in corn oil (Poiger and Schlatter 1986). Data regarding absorption of CDDs from breast milk in nursing infants are provided in Section 2.3.4.4.

Gastrointestinal absorption of radiolabeled 2,3,7,8-TCDD has been investigated in rodents. About 73.5% of the total dose of 2,3,7,8-TCDD (administered by gavage in corn oil vehicle) was absorbed in Syrian hamsters, the species most resistant to acute 2,3,7,8-TCDD toxicity (Olson et al. 1980b). In Sprague-Dawley rats given a single gavage dose of 50 µg/kg 2,3,7,8-TCDD in corn oil, at least 70% was absorbed (Piper et al. 1973). Rose et al. (1976) found a mean of 84% of a single oral gavage dose of 1 µg/kg absorbed within a day in a similar study and a steady-state body burden was achieved after dosing with 0.01, 0.1, or 1 µg/kg in corn oil, 5 days a week for 7 weeks. When ^{14}C-2,3,7,8-TCDD was fed to Sprague-Dawley rats at 0.35 µg/kg/day or 1 µg/kg/day in the diet for 42 days, about 60% of the consumed dose was absorbed (Fries and Marrow 1975). Intestinal absorption of 2,3,7,8-TCDD did not vary with age of Fischer 344 rats (13 weeks, 13 or 26 months) when *in vivo* absorption was studied with an *in situ* intestinal perfusion technique (Hebert and Birnbaum 1987). When ICR/Ha Swiss mice were given a single dose of radioactively labeled 2,3,7,8-TCDD, 67–76% of the administered dose was excreted in feces and 1–2% in urine within the first 24 hours (Koshakji et al. 1984). The authors (Koshakji et al. 1984) concluded that most of the dose was not absorbed. The more highly chlorinated CDD congeners are absorbed from the gastrointestinal tract to a lesser extent than 2,3,7,8-TCDD.

Gastrointestinal absorption of 2,3,7,8-TCDD may differ depending on the vehicle used. When hepatic concentrations were used as a measure of absorbed dose, the levels observed in rats 24 hours after 2,3,7,8-TCDD administration in 50% ethanol were higher than in an aqueous suspension of soil (Poiger and Schlatter 1980). Use of activated carbon as a vehicle almost completely eliminated 2,3,7,8-TCDD

absorption. It was further demonstrated that the absorption of 2,3,7,8-TCDD from the gastrointestinal tract of rats was . 50% less from contaminated soil than from corn oil (Lucier et al. 1986), which is supported by the finding that 2,3,7,8-TCDD-contaminated soil was less toxic to guinea pigs than an equivalent amount of 2,3,7,8-TCDD in oil (Umbreit et al. 1985). Gastrointestinal absorption of OCDD was <10% of the administered dose in Sprague-Dawley and Fischer 344 rats following single or repeated (3-week) exposures by gavage in oil vehicle (Birnbaum and Couture 1988; Norback et al. 1975). Low doses (50 µg/kg) in a *o*-dichlorobenzene:corn oil (1:1) vehicle were found to give the best oral bioavailability for this extremely insoluble compound (Birnbaum and Couture 1988). The bioavailability of CDDs (2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD) to rats was lower on fly ash (0.4% for 2,3,7,8-TCDD) as compared to extracts of the same fly ash administered in an oily vehicle (45% for 2,3,7,8-TCDD) (Van den Berg et al. 1983, 1987c). The differences in hepatic levels between fly ash- and extract-treated rats were greater for the more highly chlorinated congeners.

2.3.1.3 Dermal Exposure

No quantitative data were located regarding absorption of CDDs in humans following dermal exposure. However, based on data from studies with structurally related chemicals it is reasonable to assume that CDDs are absorbed by this route. Furthermore, data on levels of CDDs in blood from populations with above-background exposures (i.e., occupational, accidental) also suggest that dermal absorption occurs in humans. Due to the relatively low vapor pressure and high lipid solubility, dermal uptake of 2,3,7,8-TCDD in the workplace may be a significant source of occupational exposure (Kerger et al. 1995).

Kerger et al. (1995) examined the potential contribution of dermal exposure to 2,3,7,8-TCDD for three different occupational exposure scenarios: 1) trichlorophenoxy herbicide manufacturing worker (20-year exposure), 2) contract maintenance mechanic exposed by repairing a trichlorophenol reactor after an explosion accident (6-week exposure), and 3) trichlorophenoxy applicator handling only diluted trichlorophenoxy herbicides (seasonal exposure for 20 years). In their evaluation, the authors used a conceptual model of workplace exposure, dermal bioavailability/uptake calculations, and simple pharmacokinetic modeling techniques (details of the model were not provided). The contribution of background uptake of 2,3,7,8-TCDD from dietary sources in the United States was accounted for in the estimates of steady-state adipose concentrations. The results of the modeling showed that considerable occupational uptake can occur following both long-term continuous exposure and short-term high exposure. In the former case, occupational uptake can be distinguished from background exposures when

body burden is measured within a 10-year period following cessation of exposure. In contrast, seasonal exposure to dilute 2,3,7,8,-TCDD residues may result in little or no change in 2,3,7,8-TCDD body burden.

The *in vitro* penetration of ^{3}H-labeled 2,3,7,8-TCDD into human cadaver skin was studied at concentrations of 6.5 and 65 ng 2,3,7,8-TCDD/cm^2 of skin (Weber et al. 1991). Two vehicles were used: acetone to simulate exposure to 2,3,7,8-TCDD as a dry material, and mineral oil to simulate exposure in an oily medium. The experiments were conducted in intact skin and in skin with stripped stratum corneum and penetration was monitored for 30, 100, 300, and 1,000 minutes. The results showed that acetone as a vehicle allowed 2,3,7,8-TCDD to penetrate deeply into the loose surface of the lamellae of the stratum corneum, but there was little further penetration. On the other hand, mineral oil appeared to compete with lipophilic constituents of the stratum corneum for 2,3,7,8-TCDD, thus slowing its penetration even more. Removal of the stratum corneum increased the amount of 2,3,7,8-TCDD absorbed into layers of the skin. Rates of absorption were calculated in two ways: a worst case scenario where 2,3,7,8-TCDD absorbed into any layer of skin including the stratum corneum was used for analysis; and a physiological approach where only the amount of 2,3,7,8-TCDD which had penetrated beyond the epidermis into the region of dermal vascularization was considered absorbed. In the former case, the stratum corneum appeared to mediate dermal absorption of 2,3,7,8-TCDD since the rates decreased when stripped skin was exposed to 2,3,7,8-TCDD. With the physiological approach, the rate of absorption was a function of the amount applied suggesting that the rate of absorption per unit time was a first-order function. The amount of 2,3,7,8-TCDD that penetrated the skin also correlated with exposure duration. The rate of 2,3,7,8-TCDD penetration with acetone as vehicle ranged from 100 to 800 pg 2,3,7,8-TCDD per hour-cm^2 (worst-case scenario), or 6–170 pg per hour-cm^2 with the physiological approach. The corresponding values with mineral oil as a vehicle were 20–220 pg and 1.4–18 pg per hour-cm^2, respectively.

Data regarding dermal absorption of CDDs in animals are limited. When 200 pmol 2,3,7,8-TCDD was applied to the skin of Fischer 344 rats, absorption followed first-order kinetics with an absorption rate constant of 0.005 hour^{-1} (Banks and Birnbaum 1991). Within 120 hours postexposure, about 0.026 µg 2,3,7,8-TCDD was absorbed (less than 50% of the applied dose); at each interval of measurement, about 70% of detected radioactivity on the skin could be removed by swabbing with acetone. About 15% of the dose was detected in the liver of rats 24 hours after dermal exposure to 26 ng of 2,3,7,8-TCDD in 50% methanol (Poiger and Schlatter 1980). It was estimated that the amount absorbed from the dermal exposure represents .40% of the amount absorbed from an equivalent oral dose. Absorption of 2,3,7,8-TCDD was significantly reduced by application in Vaseline or polyethylene glycol and practically

eliminated in soil or activated carbon. Dermal absorption of radioactively labeled 2,3,7,8-TCDD in soil vehicle was reported to be only 1% of the administered dose during a 24-hour contact in rats (Shu et al. 1988). The dermal absorption of 2,3,7,8-TCDD after 4 hours of contact was about 60% of that after 24-hour contact. The uptake was not influenced by the 2,3,7,8-TCDD concentration in soil, nor were there any differences between normal and hairless rats.

Dermal absorption in rats was found to be age-related. Banks et al. (1990) found that in Fischer 344 rats, the percutaneous absorption was decreased in middle-aged (36-week-old) and senescent (120-week-old) rats compared to that in young adults (10-week-old) 72 hours after application of a dose of 40 nmol (approximately 12.9 μg) of ^{3}H-labeled 2,3,7,8-TCDD. The authors suggested a decrease in blood flow through the skin between 3 and 4 months of age as a possible explanation for their findings. In a subsequent and similar study, the same group of investigators examined the dermal absorption of 2,3,7,8-TCDD in 3-, 5-, 8-, 10-, and 36-week-old Fischer 344 rats 72 hours after application of 200 pmol 2,3,7,8-TCDD in acetone (Banks et al. 1993). Dermal absorption was greatest in 3-week-old rats (approximately 64% of the applied dose), decreased to about 40% of the applied dose in 5-, 8-, and 10-week-old rats and to about 22% in 36-week-old rats. In each age group, 70–80% of the radioactivity remaining at the application site 72 hours after dosing could be removed with acetone swabs.

2.3.2 Distribution

As discussed in Section 2.1, occupational or environmental human exposure to CDDs is not readily classifiable as to route of exposure. Human data regarding distribution obtained at autopsy indicated that accumulation in the liver following low levels of exposure is based in part on lipid solubility (Leung et al. 1990a). However, this may not be the case with higher exposure levels that cause hepatic enzyme induction (see Section 2.4.1). When human hepatic and adipose tissues were examined for the presence of 2,3,7,8-TCDD, the concentration detected in the liver was about 1/10 of that in the adipose tissue on a whole-tissue-weight basis. However, on the basis of the total tissue lipid, the concentration in adipose tissue lipid was one-half that in the liver lipid (Thoma et al. 1990). It was further demonstrated that over a wide range of concentrations, the serum 2,3,7,8-TCDD levels highly correlated with adipose tissue 2,3,7,8-TCDD levels when both are expressed on a lipid weight basis (Patterson et al. 1988). Adipose tissue serves as a storage depot for 2,3,7,8-TCDD in the body, and detectable levels (up to 20.2 ppt) were found in the general population with no known risk of high exposure to CDDs (Andrews et al. 1989). An average concentration of 2,3,7,8-TCDD in serum lipid of 5.38 ppt has been estimated for the U.S.

population (Orban et al. 1994). The distribution of highly chlorinated CDDs among tissue lipid fractions is not equal. For example, the distribution of OCDD is 12:1 (Thoma et al. 1990) between liver and adipose tissue lipid factions and 2:1 between serum and adipose tissue lipid fractions (Schecter et al. 1990).

Increased adipose tissue levels of CDDs were reported in populations with known high residential or occupational exposure (Beck et al. 1989c; Fingerhut et al. 1989; Patterson et al. 1989b; Schecter et al. 1994). For example, high levels of 2,3,7,8-TCDD were found in fat (42–750 ppt) and serum lipid (61–1,090 ppt) of Missouri chemical workers (Patterson et al. 1989b). Measurable CDDs and CDFs levels were reported in the liver tissue of human stillborn neonates suggesting that the transplacental intrauterine transfer of these persistent chemicals resulted from environmentally exposed mothers (Schecter et al. 1990). In addition, CDDs are distributed to human milk (i.e., Fürst et al. 1994; Schecter et al. 1987a, 1987b, 1989e) and numerous studies have published concentrations of various congeners in human milk samples (see section 5.5.1). Levels of CDDs in human milk have been found to be significantly and positively associated with of proximity of residence to waste sites and to dietary fat intake per week (Schaud et al. 1995).

2.3.2.1 Inhalation Exposure

The tissue distribution of 2,3,7,8-TCDD-derived radioactivity was recently examined in male Fischer 344 rats 3 days after intratracheal application of a single dose of 0.32 µg 2,3,7,8-TCDD/kg (Diliberto et al. 1996). The liver and adipose tissue were the major tissue depots for 2,3,7,8-TCDD-derived radioactivity with 33 and 15% of the applied dose distributing to these respective tissues. The skin (ear) and muscle followed with 4.3 and 1.3%, respectively. All other tissues had less than 0.5% of the administered dose. The 2/1 liver/adipose ratio was in contrast to the approximately 1/1 ratio found after gavage administration of the same dose.

2.3.2.2 Oral Exposure

Following an ingested dose of ^{3}H-2,3,7,8-TCDD of 0.00114 µg/kg by a volunteer, the concentration of 2,3,7,8-TCDD in the adipose tissue were 3.09 and 2.86 ppt at 13 and 69 days following exposure, respectively (Poiger and Schlatter 1986). The authors estimated that about 90% of the body burden was distributed to the fatty tissue. Increased radioactivity was detected in the blood only during the first 2 days

postexposure; no radioactivity was detected in serum lipid after 5 days, but was in the feces for several months.

Studies in animals have shown that 2,3,7,8-TCDD distributes preferentially to the liver and adipose tissue. In Sprague-Dawley rats, the highest levels of radioactivity (expressed as percentage of dose per gram of tissue) were located in the liver (3.18, 4.49, and 1.33% at days 3, 7, and 21 post-exposure, respectively) and adipose tissues (2.6, 3.22, and 0.43% at days 3, 7, and 21, respectively) following a single oral dose of labeled 2,3,7,8-TCDD at 50 µg/kg (Piper et al. 1973). Much smaller amounts were found in muscles, testes, lungs, stomach, and other organs. In male Fischer 344 rats administered a single gavage dose of 0.32 µg 2,3,7,8-TCDD/kg, 24.4 and 26.2% of the administered dose was found in the liver and adipose tissue, respectively, 3 days after dosing (Diliberto et al. 1996); skin and muscle had 7.3 and 1.8%, respectively. 2,3,7,8-TCDD accumulated mainly in the liver and adipose tissue, with smaller amounts in the brain of pregnant Wistar rats after 10 daily doses of 2 µg/kg (Khera and Ruddick 1973). Similarly, the highest levels of radioactivity were found in the liver, adipose tissue, and the adrenals of Golden Syrian hamsters after a single gavage dose of 650 µg/kg labeled 2,3,7,8-TCDD (Olson et al. 1980b). In addition, about 36% of the total radioactivity administered remained in the adipose tissue by day 45 postexposure in Hartley guinea pigs; only about 7% (each) was found in the liver, muscles, and carcass (Olson 1986). Essentially all of the administered dose was unchanged 2,3,7,8-TCDD. When pregnant NMRI mice were exposed to a single oral, intraperitoneal, or subcutaneous dose of 2,3,7,8-TCDD, hepatic levels were about the same, indicating that there is no major first pass effect after oral 2,3,7,8-TCDD exposure (Nau and Bass 1981). Liver, then adipose tissue and skin, were the major depots of OCDD in Fischer 344 rats treated with single oral doses of this congener (Birnbaum and Couture 1988).

The dose- and time-dependent tissue distribution of 2,3,7,8-TCDD in mice has been recently examined (Diliberto et al. 1995). Female B6C3F_1 mice were administered a single dose of 0.1, 1, or 10 µg [^{3}H]-2,3,7,8-TCDD/kg by gavage in corn oil and the distribution of radioactivity was followed in 18 tissues for up to 35 days after dosing. The results showed dose-dependent distribution of 2,3,7,8-TCDD-derived radioactivity in all tissues. The highest concentrations of radioactivity were found in liver and adipose tissues, and both tissues accounted for 50% of the body burden. Relatively high concentrations of 2,3,7,8-TCDD-derived radioactivity were also found in skin, adrenal glands, thyroid, pancreas, olfactory epithelium, spleen, mesenteric lymph nodes, thymus, lung, and bone marrow. The liver concentration of radioactivity increased disproportionally with increasing doses, whereas relative concentration and percentage dose/total tissue in extrahepatic tissues decreased with increasing dose and over time.

Liver/adipose tissue concentration ratios were shown to be dose- and time-dependent. At the low-, mid- and high-dose, the ratios ranged from 0.6 to 0.2, 2.3–0.5, and 3.1–1.4 over time, respectively. This variation over time was thought to have been due to redistribution of 2,3,7,8-TCDD between the two storage sites and/or hepatic metabolism and subsequent excretion.

The effect of age of the animal on 2,3,7,8-TCDD tissue distribution has also been examined. Pegram et al. (1995) administered a single dose of 0.015, 0.5 or 15 µg [^{3}H]2,3,7,8-TCDD/kg to 10-week- and 28-month-old male C57BL/6N mice and monitored 2,3,7,8-TCDD-derived radioactivity in blood, liver, skin, kidney, and muscle 7 days after dosing. The results showed that in young mice given the low- and high-dose, the concentration of 2,3,7,8-TCDD in blood relative to all other tissues was significantly greater than in older mice. Also, in older mice, the concentration of 2,3,7,8-TCDD in skin and the percentage of the dose in the skin were greater than in the young mice. The same trend was observed in kidney and muscle. The concentration of 2,3,7,8-TCDD in liver, as well as the percentage of the dose in the liver, were greater in young than old animals at both the mid- and high-doses. In both young and old mice the ratios of liver to adipose tissue increased with increasing doses. According to the authors, the higher hepatic concentration of 2,3,7,8-TCDD in young mice could be due to the old mice having a larger fat compartment, such that the hepatic 2,3,7,8-TCDD sequestering action of CYP1A2 or other inducible binding factors may have been less effective in the more obese older mice. In addition, decreased perfusion in the liver and adipose compartments in the old mice may have limited the effectiveness of hepatic 2,3,7,8-TCDD accumulation. The greater accumulation of 2,3,7,8-TCDD in the skin, muscle, and kidney from old mice were attributed to altered perfusion and possibly greater lipid infiltration in these tissues.

The subcellular distribution of 2,3,7,8-TCDD-derived radioactivity in the liver, lungs, and kidneys from female Sprague-Dawley rats and B6C3F1 mice was studied by Santostefano et al. (1996). In the liver of rats given a single oral dose of 0.1, 1, or 10 µg [^{3}H]-2,3,7,8-TCDD/kg, radioactivity accumulated equally in the supernatant (S9, cytosol, and microsomes) and pellet (P9, nucleus, lysosomes, and mitochondria) fractions; within the S9 fraction, accumulation was predominantly in the microsomal fraction. In contrast, in kidneys and lungs radioactivity accumulated preferentially in P9, but radioactivity detected in S9 was mostly in the cytosolic fraction. The pattern of distribution of radioactivity in liver and lungs from mice was similar to that found in rats, but in mice kidneys, 2,3,7,8-TCDD detected in S9 was equally distributed between the microsomal and cytosolic fractions. Accumulation of 2,3,7,8-TCDD in the various fractions in this single-dose study was not dose-dependent. The investigators also conducted a 17-week oral dosing study in B6C3F1 mice given 1.5 or 150 ng/kg that showed that increasing the dose resulted in equal

accumulation between liver S9 and P9 fractions, whereas the kidney P9 had the most radioactivity regardless of the dose. In addition, liver S9 accumulated 2,3,7,8-TCDD in the microsomal fraction, whereas kidney S9 did it predominantly in the cytosol. These results are consistent with the hypothesis that hepatic microsomal sequestration of 2,3,7,8-TCDD is mediated by cytochrome P-4501A2 (CYP1A2), a dioxin-inducible protein. This hypothesis was subsequently confirmed by experiments in transgenic mice lacking expression of CYP1A2 (CYP1A2-/-) (Diliberto et al. 1997). These mice, as judged by 2,3,7,8-TCDD liver/fat concentration ratios, failed to sequester 2,3,7,8-TCDD in the liver after administration of a single dose of 2,3,7,8-TCDD.

Intermediate-duration exposure to 2,3,7,8-TCDD in the feed has been shown to produce higher liver accumulation in male (85%) than in female rats (70%) (Fries and Marrow 1975). The percentage retained was related to intake, and at steady state, the total amount retained was about 10.5 times the average daily intake.

Intermediate-duration studies have also been conducted with radioactively labeled OCDD. OCDD had similar patterns of distribution and similar half-lives as 2,3,7,8-TCDD in Sprague-Dawley (Norback et al. 1975) and Fischer 344 rats (Birnbaum and Couture 1988; Birnbaum et al. 1989a). Most of the absorbed amount (50–97%) was found in the liver and was associated with the microsomal fractions. Skin- and adipose-tissue levels were much lower. Radioactivity was also detected in the kidneys, heart, testes, skeletal muscle, and serum.

2.3.2.3 Dermal Exposure

Male Fischer 344 rats absorbed 40% of a single dermal dose of 0.32 µg of radioactive 2,3,7,8-TCDD/kg over a period of 120 hours after dosing (Banks and Birnbaum 1991). The major depots for 2,3,7,8-TCDD-derived radioactivity were the liver and adipose tissue. Seventy-two hours after dosing, the liver and adipose tissue retained approximately 21 and 8% of the administered dose, respectively. Distribution to the liver increased significantly between 4 and 8 hours and between 12 and 72 hours after dosing. Distribution in fat increased significantly between 12 and 120 hours after dosing. Skin and muscle accumulated considerably less 2,3,7,8-TCDD-derived radioactivity than liver and fat. Within 120 hours of dosing, less than 4% of the administered dose was found in either of these tissues. When 2,3,7,8-TCDD was dermally applied to HRS/J hairless mice for an intermediate duration, about 5–6% of the total administered dose (0.0025–0.01 µg/kg, 2 days a week, for 20 weeks) was detected in the liver (Hebert et al. 1990).

2.3.3 Metabolism

No data were located regarding metabolic pathways of CDDs in humans. However, there is some evidence that 2,3,7,8-TCDD is partially excreted in the feces in the form of metabolites (Wendling et al. 1990).

Studies in animals indicate that 2,3,7,8-TCDD is metabolized slowly in mammals (Koshakji et al. 1984). Metabolic transformation by phase I metabolizing enzymes includes oxidation and reductive dechlorination, as well as oxygen bridge cleavage. This is followed by conjugation reactions catalyzed by phase II type enzymes, which facilitate excretion by adding more polar groups to the molecule. For example, a study in guinea pigs showed that only 28% of the radioactivity in the tissues 45 days following exposure to ^{3}H-2,3,7,8-TCDD was in the form of metabolites (Olson 1986). Results from high performance liquid chromatography (HPLC) suggested the presence of at least five ^{3}H-labeled metabolites of 2,3,7,8-TCDD, but their structure was not established. The results indicated that in the guinea pig, the metabolites of 2,3,7,8-TCDD may not leave the body rapidly. In rats and hamsters, metabolism appears to be required for urinary and biliary excretion (Olson et al. 1980a). Metabolites of 2,3,7,8-TCDD are not generally detected in tissues, suggesting that for most species, 2,3,7,8-TCDD is readily eliminated following metabolism. An *in vitro* study with isolated rat hepatocytes identified 1–hydroxy-2,3,7,8-TCDD and 8-hydroxy-2,3,7-TrCDD as metabolites (Sawahata et al. 1982). 2-Hydroxy-1,3,7,8-TCDD was found to be the major metabolite of 2,3,7,8-TCDD in dogs but not in rats (Poiger et al. 1982). The metabolites from dogs administered to rats were eliminated as conjugates in the bile (Weber et al. 1982). Self induction of 2,3,7,8-TCDD metabolism was reported in both species (Poiger and Schlatter 1985; Weber et al. 1982). A single 10 µg/kg dose of unlabeled 2,3,7,8-TCDD 9 days prior to administration of ^{3}H-2,3,7,8-TCDD resulted in a doubling of the amount of radioactivity eliminated in the bile of dogs. When the 2,3,7,8-TCDD metabolites, 2-hydroxy-2,3,7-TrCDD and 2-hydroxy-1,3,7,8-TCDD, were synthesized and injected intraperitoneal into Wistar rats, no toxic effects were observed (Mason and Safe 1986). This supports the observation that the extract from the bile of 2,3,7,8-TCDD-treated dogs is about 100 times less toxic to rats and guinea pigs than pure 2,3,7,8-TCDD (Poiger et al. 1982). The lack of toxicity of the 2,3,7,8-TCDD metabolites suggests that autoinduction of its own metabolism in animals is a detoxification mechanism.

Data regarding other 2,3,7,8-substituted CDDs are limited. Wacker et al. (1986) found at least three phenolic radiolabeled metabolites of ^{14}C-1,2,3,7,8-PeCDD in rat bile after treatment with glucuronidase and methylation, indicating the probability of formation of hydroxymetabolites. Results from studies in

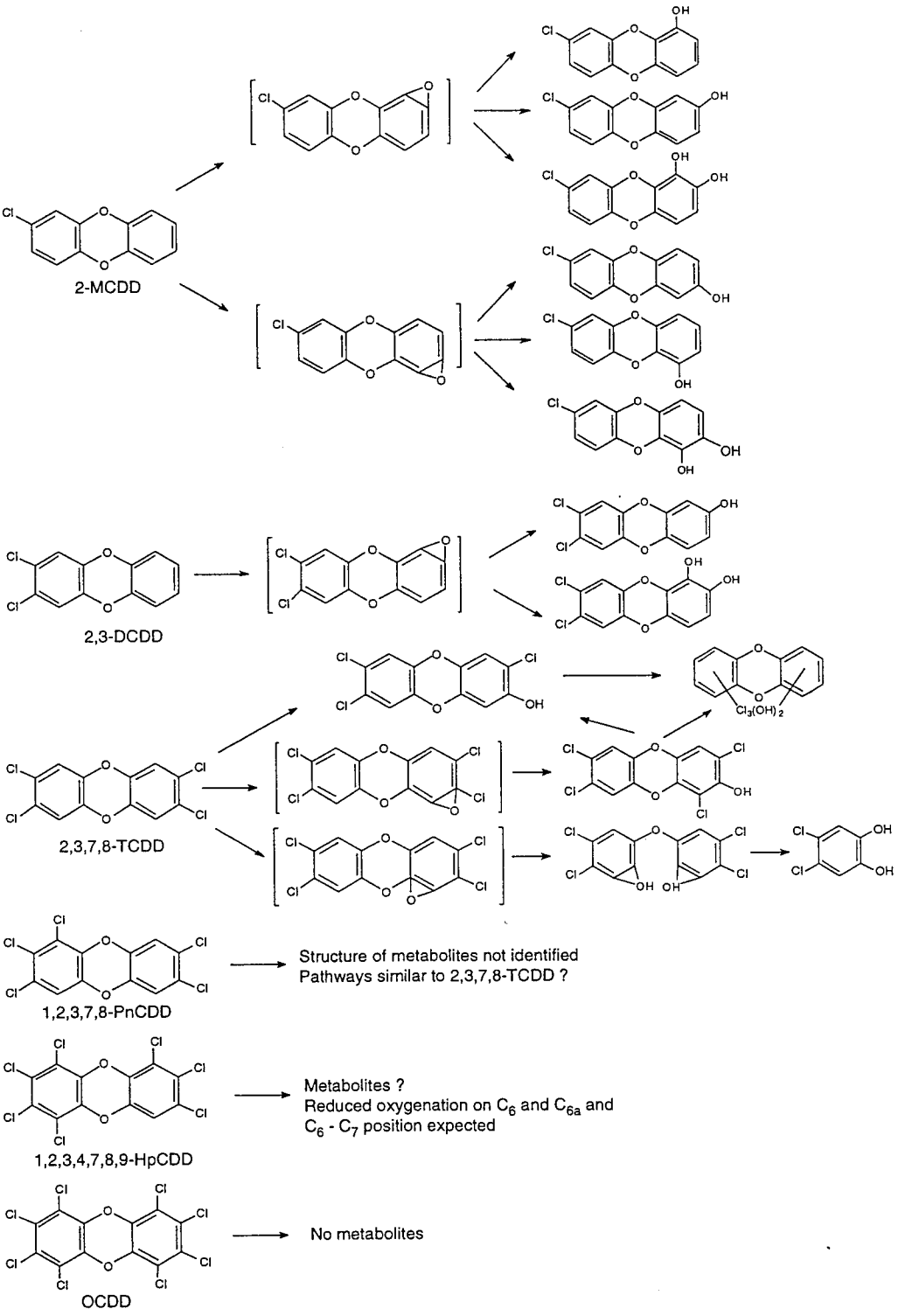
rats revealed no metabolites of OCDD, as expected from the fully chlorinated molecule (Birnbaum and Couture 1988; Tulp and Hutzinger 1978).

CDDs induce both phase I and phase II drug-metabolizing enzymes including AHH, EROD, ACOH, glucuronosyl transferase, glutathione S-transferase, and DT-diaphorase (Van den Berg et al. 1994). These enzymes are responsible for the metabolism of a variety of exogenous and endogenous substances. Pretreatment of C57BL/6J mice with 2,3,7,8-TCDD increased hepatic accumulation of a subsequent radiolabeled dose (total liver burden increased about 50%), whereas distribution to the kidney, fat, heart, lung, and gastrointestinal tract were reciprocally decreased (Curtis et al. 1990). The data indicated that an inducible, saturable system is involved in 2,3,7,8-TCDD toxicokinetics. The pretreatment, however, did not alter the hepatic metabolism of 2,3,7,8-TCDD in exposed mice. Similarly, the rate of metabolism of 2,3,7,8-TCDD in hepatocytes from 2,3,7,8-TCDD-pretreated (induced) guinea pigs and mice was unchanged from that in untreated animals (Olson and Wroblewski 1985; Shen et al. 1989; Wroblewski and Olson 1985). In contrast, the rate of metabolism in hepatocytes from 2,3,7,8-TCDD-pretreated rats was 3.2-fold greater than the rate in hepatocytes from control rats and about 9 times greater than in hepatocytes from 2,3,7,8-TCDD-pretreated guinea pigs. The difference between the 2,3,7,8-TCDD ability to induce its own rate of metabolism in rats and guinea pigs could be a factor in the difference between the susceptibility to 2,3,7,8-TCDD-induced toxicity in these two species, because the parent compound rather than metabolites is the toxic agent (Poland and Glover 1979). A generalized scheme of metabolic pathways for CDDs based on information from *in vivo* mammalian studies was proposed by Van den Berg et al. (1994) and is presented in Figure 2-3.

2.3.4 Elimination and Excretion

A median half-life of 7.1 years was estimated for 2,3,7,8-TCDD in a group of 36 Vietnam veterans (CDC 1987; Pirkle et al. 1989). The calculation was based on the decrease of 2,3,7,8-TCDD serum levels that

Figure 2-3. A Generalized Scheme of Pathways for the Biotransformation of CDDs Based on Information from *In Vivo* Mammalian Studies



Source: adapted from Van der Berg et al. 1994

were measured in these individuals in 1982 and again in 1987. The individual half-life values varied from 2.9 to 26.9 years. In an expanded half-life study of 343 Vietnam veterans participating in Operation Ranch Hand, which included the subjects of the Pirkle et al. (1989) study, a half-life estimate of 8.7 years (95% CI of 8.0–9.5 years) was calculated (Michalek et al. 1996). The half-life estimate was calculated using 2,3,7,8-TCDD levels in blood samples collected in 1982, 1987, and 1992. An earlier study of these subjects (Wolfe et al. 1994), which used data from two blood collection periods (1982 and 1987) estimated a half-life of 11.3 years (95% CI of 10–14.1 years). This half-life of 11.3 years was considered too high because it was based on restricted analysis of veterans with 2,3,7,8-TCDD levels above 10 ppt. By conditioning the data to lie above a line with slope equal to the negative of the decay rate, the analysis yielded a revised half-life of 8.7 years. The Michalek et al. (1996) half-life estimate of 8.7 years supersedes other estimates for this group of veterans because it includes an additional measurement of serum lipid 2,3,7,8-TCDD levels and controls for potential biases.

Several other studies have calculated 2,3,7,8-TCDD half-lives. A mean half-life of 5.8 years was estimated from repeated samples from 29 BASF AG facility workers whose initial 2,3,7,8-TCDD serum lipid concentrations ranged from 29 to 553 ppt (Ott and Zober 1996). In a study of 48 German workers at a pesticide facility who were exposed to a mixture of CDDs/CDFs, a median half-life of 7.2 years was estimated for 2,3,7,8-TCDD (Flesch-Janys et al. 1996). Needham et al. (1994) estimated a half-life of 8.2 years in 27 Seveso residents with initial serum 2,3,7,8-TCDD levels of 130 to 3,830 ppt. Using data from a human subject ingesting a single dose of 1.14 ng/kg 2,3,7,8-TCDD, Poiger and Schlatter (1986) calculated a half-life of 2,120 days (5.8 years). Geyer et al. (1986a) noted that they calculated a half-life of 3.5-6.9 years, but did not describe the basis of this estimation. Overall, there is good agreement between the 2,3,7,8-TCDD half-lives estimated in 4 different populations (Vietnam veterans, BASF AG cohort, German pesticide workers, and Seveso residents); the half-lives ranged from 5.8 to 8.7 years (Flesch-Janys et al. 1996; Michalek et al. 1996; Needham et al. 1994; Ott and Zober 1996). Several studies have found correlations between percentage of body fat and 2,3,7,8-TCDD elimination half-times (Flesch-Janys et al. 1996; Michalek et al. 1996; Ott and Zober 1996; Wolfe et al. 1994). Ott and Zober (1996) estimated half-lives of 5.1 and 8.9 years in subjects with 20 and 30% body fat, respectively.

There are limited data available on the elimination of other CDD congeners in humans. In the Flesch-Janys et al. (1996) study of 48 workers at a German pesticide facility, elimination half times were estimated for several CDD congeners. The estimated half-lives were 15.7 years for 1,2,3,7,8-PeCDD, 8.4 years for 1,2,3,4,7,8-HxCDD, 13.1 years for 1,2,3,6,7,8-HxCDD, 4.9 years for 1,2,3,7,8,9-HxCDD, 3.7 years for

1,2,3,4,6,7,8-HpCDD, and 6.7 years for OCDD. In a study of six German workers with high CDD/CDF body burdens, elimination half-lives corrected for alterations in body weight ranged from 3.5 years for 1,2,3,4,6,7,8-HpCDF to 7.9 years for 2,3,7,8-TCDD and 15 years for 1,2,3,4,7,8-HxCDD (Rohde et al. 1997). In the same study, half-lives for elimination due only to fecal excretion ranged from 10 years for OCDD to 22 years for 2,3,7,8-TCDD and 27 years for 1,2,3,7,8-PeCDD. The half-lives for 2,3,4,7,8-PeCDF in humans exposed to contaminated rice oil in the Yusho incident range from 2 to 30 years, and were inversely dependent on adipose tissue concentrations above approximately 10 ng/kg body weight (i.e., the higher the body burden, the faster the elimination) (Ryan et al. 1993a).

Elimination of CDDs through lactation is discussed in Section 2.3.4.4.

2.3.4.1 Inhalation Exposure

In male Fischer 344 rats administered a single intratracheal dose of 0.32 µg labeled 2,3,7,8-TCDD/kg, feces was the major route of excretion over a 3-day period after dosing (Diliberto et al. 1996). The cumulative excretion of 26.3% of the administered dose was observed over 3 days following exposure. Approximately 4% of the dose was excreted in the feces on day 3. The cumulative urinary excretion was only 1.3% of the administered dose.

2.3.4.2 Oral Exposure

The half-life for elimination of a single oral dose of 0.00114 µg/kg ^{3}H 2,3,7,8-TCDD in a human volunteer was calculated as 5.8 years (Poiger and Schlatter 1986). The excretion in feces was high during the first few days (up to day 6) probably because of elimination of unabsorbed material. During these first few days, about 12% of the administered dose was excreted. However, during days 7–125 only about 3.5% of the administered dose was eliminated. Urinary levels of radioactivity did not exceed the background levels.

Studies in animals indicated that elimination of 2,3,7,8-TCDD is a relatively slow process. However, the results showed a great variability among species. The half-life for 2,3,7,8-TCDD elimination was 14.95 days in Syrian hamsters (Olson et al. 1980b), 12 and 14 days in male and female Sprague-Dawley rats, respectively (Fries and Marrow 1975), 17 days in male Sprague-Dawley rats in another study (Piper et al. 1973), and 94 days in guinea pigs, the most sensitive species to the acute toxicity of 2,3,7,8-TCDD (Olson 1986). In contrast, the elimination half-life was 391 days in monkeys chronically exposed to low

doses of 2,3,7,8-TCDD in the feed (Bowman et al. 1989b). A similar half-life of about 1 year was observed in monkeys after a single-dose exposure (McNulty et al. 1982). In addition, studies of 2,3,7,8-TCDD half-life in highly exposed rats (Abraham et al. 1988), rhesus monkeys (McNulty et al. 1982) and marmoset monkeys showed that rates of excretion decreased with dose.

The clearance of radioactivity after oral exposure to labeled 2,3,7,8-TCDD followed first-order kinetics in most studies. Fecal elimination was the major route, though excretion in the urine, expired air, and milk was also reported.

When Sprague-Dawley rats were given radioactively labeled 2,3,7,8-TCDD, a total of 53% of the administered radioactivity was excreted by feces in the first 21 days (Piper et al. 1973). Elimination of 2,3,7,8-TCDD-derived radioactivity in urine and expired air was 13 and 3% of the administered dose, respectively. Thirty-two percent of a single gavage dose of 0.32 µg of 2,3,7,8-TCDD/kg was eliminated in the feces of male Fischer 344 rats over a 3-day period after dosing (Diliberto et al. 1996). Only 1.4% of the administered dose was excreted in the urine over the same period. About 20–30% of the total oral 2,3,7,8-TCDD dose was eliminated in the bile of cholecystectomized and cannulated dogs (Poiger et al. 1982). In addition, excretion of unchanged 2,3,7,8-TCDD in milk was demonstrated in NMRI mice (Nau et al. 1986) and in monkeys (Bowman et al. 1989b), after oral exposure.

Of the other congeners, several have been studied. An elimination half-life of 29.5 days was estimated for 1,2,3,7,8-PCDD in Sprague-Dawley rats following a single oral exposure (Wacker et al. 1986). OCDD was more persistent in Fischer 344 rats with an estimated elimination half-life of 3–5 months following 10 daily oral doses (Birnbaum and Couture 1988). These congeners were excreted primarily in the feces following biliary elimination as metabolites (1,2,3,7,8-PCDD, at least three phenolic metabolites) or parent compound. A 13-week dosing study in which Sprague-Dawley rats were administered various mixtures of CDDs estimated liver half-lives of 14.5, 29.3, 45.6, and 100 days for 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD, respectively (Viluksela et al. 1998a).

2.3.4.3 Dermal Exposure

Within 120 hours after dermal administration of 0.32 µg/kg 2,3,7,8-TCDD to the clipped back skin of male Fischer 344 rats, 4% of the administered dose was excreted in the feces and <1% was excreted in the urine (Banks and Birnbaum 1991). The rate of 2,3,7,8-TCDD elimination significantly increased over time.

2.3.4.4 Transfer of CDDs Through the Placenta and Breast Milk

CDDs are lipophilic compounds which can concentrate in maternal milk. Therefore, lactation provides an efficient mechanism for decreasing the body burden of these compounds (Schecter and Gasiewicz 1987a). CDD levels in breast milk samples from 193 German women ranged from 2.5 to 47 ng TEQ/kg milk fat (mean of 13 ng/kg) (Fürst et al. 1989b). More than 50% of the total CDDs detected in samples was represented by OCDD, which was detected at a mean concentration of 195 ng/kg milk fat (range, 13–664 ng/kg). The amounts of other congeners in human milk decreased with decreasing chlorination; the mean concentration of 2,3,7,8-TCDD in milk fat was 2.9 ng/kg (range, <1–7.9 ng/kg). A more recent analysis of 526 individual milk samples from the German general population revealed a mean 2,3,7,8-TCDD concentration of 3.2 ng/kg milk fat (Fürst et al. 1994). The analysis also showed the presence of only 2,3,7,8-chlorine-substituted CDD congeners. OCDD was the most concentrated congener with a mean level of 208 ng/kg milk fat. In general, the levels in milk decreased with decreasing degree of chlorination from octa- to tetra-CDD. Schecter and coworkers have published information on levels of dioxins in human breast milk from various countries (Schecter et al. 1989d, 1989e) (see also Section 2.6.1). In general, milk samples from industrial countries had higher CDD levels than those from less developed countries. Representative mean levels of CDDs in samples of human breast milk from various countries are presented in Table 2-6.

Fürst et al. (1989b) also found that the levels of CDDs found in the milk of mothers breast-feeding their second child were about 20–30% lower than in those breast-feeding their first child. It was further noted that the highest excretion of CDDs was during the first few weeks after delivery. The sharpest decline was observed with OCDD; its excretion was reduced by half between the 1st and 5th week of lactation. In contrast, there was no significant decline in total HxCDDs in milk during the first year of lactation. The concentration of 1,2,3,4,6,7,8-HpCDD in milk fat showed a steady decline over the 1-year period, but its levels stayed relatively high. 2,3,7,8-TCDD represented the smallest portion of the total CDDs, and its levels in milk continuously declined over the year of lactation. Levels of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD were measured in a mother of twins prior to nursing and after 2 years of nursing (Schecter et al. 1996a). There was a 49.5% decrease in the total amount of CDDs in the lipid fraction of the breast milk. 2,3,7,8-TCDD had the largest percent decline in CDD levels, a decrease of 83.9%. A 52.4% decrease in maternal serum lipid levels of total CDD was also observed; the largest percent decline was an 86.8% decline in 1,2,3,7,8-PeCDD levels.

Table 2-6. Mean Levels of CDDs in Breast Milk (ng/kg milk fat)

	The Netherlands[a] N=35	Canada[b] N=96	USA[c] N=42	Germany[d] N=526	Siberia[c] N=23	United Kingdom[e] N=57	South Vietnam (1973)[c] N=7	Cambodia[c] N=8
2,3,7,8-TCDD	3.8	2.3	3.3	3.2	2.7	5.6	131.0	0.49
1,2,3,7,8-PeCDD	10.6	4.8	6.7	10.1	3.3	13	ND	1.6
1,2,3,4,7,8-HxCDD	1.3	34.6[f]	4.9	8.4	1.6	62.0[f]	70.0[f]	0.6
1,2,3,6,7,8-HxCDD	49.1		30.5	35.8	5.6			3.4
1,2,3,7,8,9-HxCDD	6.5	6.4	6.2	6.4	1.2	8.3		1.1
1,2,3,4,7,8,9-HpCDD	54.3	40.5	42.0	14.2	8.1	10.5	99.0	11.0
OCDD	297.5	131.7	233.0	207.9	50.2	287	494.0	59.0
Total TEQ for CDDs only[g]	15.6	9.34	11.5	13.9	5.3	20.1	139.5	20.0

[a] Pluim et al. 1994a
[b] Dewailly et al. 1991
[c] Schecter et al. 1991a
[d] Fürst et al. 1994
[e] Duarte-Davidson et al. 1992
[f] For unseparated congeners
[g] See Section 2.5 for additional information

ND = not detected; TEQ = toxicity equivalency

Several studies have shown that CDDs in breast milk are readily absorbed by nursing infants. In a 19-week-old nursing infant, absorption was estimated as the difference between ingestion and the amount of CDDs found in the feces over a period of 12 days (McLachlan 1993). The mother was 32 years old and nursing for the first time. Several CDD congeners were determined in the milk: 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, three hexacloro-substituted congeners, 1,2,3,4,6,7,8-HpCDD, and OCDD. The percentage of dose absorbed ranged from 90 to 95% except for the hepta-substituted congeners and OCDD which exhibited absorption rates of 61 and 23%, respectively. The percentage of the dose absorbed increased slightly if corrections were made for background levels in the diapers. Similar results were reported by Pluim et al. (1993b) who measured the amount of CDDs consumed via breast milk and excreted in the feces in 3 infants at the ages of 4, 8, and 12 weeks. Because of the high content of CDDs of the diapers relative to the feces, the percentage of dose absorbed was not determined. However, the results showed that, with the exception of OCDD, the bioavailability from breast milk was greater than 95%. At 4 weeks of age, the average cumulative intake of CDDs from breast milk was 132.1 pg TEQ per kg body weight. Of these, 37.4 corresponded to 2,3,7,8-TCDD, 46.2 to 1,2,3,7,8-PCDD, and 24.4 to 1,2,3,6,7,8-HxCDD. With the inclusion of CDFs, the total TEQ at 4 weeks was approximately 257 pg/kg body weight. Exposure to CDDs and CDFs from lactation decreased at 8 and 12 weeks mainly due to a decrease in their concentration in whole breast milk which resulted from a reduced fat content of the milk (the depletion of body burden of the mother while nursing may have also contributed). Abraham et al. (1994, 1996) and Dahl et al. (1995) also reported almost complete absorption of lower chlorinated CDDs and CDFs in breast-fed infants during the first year of life. It was also noticed that intake of CDDs and CDFs was up to 50 times higher in breast-fed infants compared with a formula-fed infant (Abraham et al. 1996). The latter study further showed that despite much lower intake of CDDs and CDFs after weaning, the concentration of these compounds in stool fat did not decrease substantially, suggesting that concentration in fecal fat more or less reflect that in body fat. Also, at 11 months of age, TEQ concentrations in blood from formula-fed infants were less than 25% of maternal values and about 10 times lower than in infants breast-fed for 6-7 months (Abraham et al. 1996).

Schecter et al. (1996b) recently presented data on the levels of CDDs and CDFs in human fetuses (8–14 weeks gestational age with placenta removed) and in placentas from women from the general population who had normal deliveries. On a lipid basis, the total TEQs (CDDs plus CDFs) in a pool of 14 placentas was 10.1 ng/kg; half this amount (5.3 ng/kg) was measured in a pool of 10 fetuses. In an analysis of 43 samples of human milk, Schecter et al. (1996b) found that the total concentration of CDDs and CDFs was 16.7 ng/kg (expressed as TEQ). The authors also calculated that the TEQ body burden for

the pooled fetal tissue was 0.034 ng/kg body weight; for pooled placentas, they calculated a total TEQ of 0.086 ng/kg wet weight. These results suggest that the transfer of CDDs to the fetus may be somewhat limited.

The influence of maternal transfer (placental and via breast milk) of CDDs/CDFs on the body burden of newborns and infants was further investigated by Kreuzer et al. (1997). These investigators also developed a pharmacokinetic model for 2,3,7,8-TCDD that allowed them to simulate body and tissue burden for the entire human lifetime as a function of 2,3,7,8-TCDD uptake from contaminated nutrition. On a lipid basis, the concentrations of 2,3,7,8-TCDD in adipose tissue and liver of breast-fed infants who died of sudden infant death syndrome were 0.4–4 ppt and 0.5–4 ppt, respectively. The corresponding values in nonbreast-fed infants were 0.2–0.8 ppt and 0.3–0.7 ppt. Similar values were detected in adipose tissue and livers of three stillborns, confirming the placental transfer of these chemicals to the fetus. The model developed by Kreuzer et al. (1997) reflected sex- and age-dependent changes in body weight, volumes of liver, adipose and muscle tissue, food consumption, and excretion of feces and was used to predict the half-life of elimination of 2,3,7,8-TCDD and its concentrations in adipose tissue, blood, liver, and feces at different ages. Also, the influence of breast-feeding on the 2,3,7,8-TCDD burden of the mother, her milk, and her child was simulated. The authors used their own data, as well as those from others, to validate the model. For nonbreast-fed infants, the model predicted a decrease in the concentration of 2,3,7,8,-TCDD in lipids during the first year, and this was supported by the empirical data. For infants exclusively breast-fed, the model predicted an increase in 2,3,7,8-TCDD burden followed by a decrease after weaning, and this was also confirmed by the measured data. Model validation of 2,3,7,8-TCDD concentrations in liver for the 20 infants investigated and in adipose tissue, blood, and feces for data in infants published by others showed good agreement between the simulated and experimental values. Since one of the model's assumption was that the concentration of 2,3,7,8-TCDD in fecal lipids reflected the concentration in lipids of the organism, the good correlation between predicted and empirical data validated the assumption. Under the assumption that the 2,3,7,8-TCDD concentration in lipids of breast milk equals the concentration in the maternal organism, the model predicted a value of 2.23 ng 2,3,7,8-TCDD/kg lipids for the beginning of the nursing period. The model further predicted that the concentration of 2,3,7,8-TCDD in milk decreases with duration of breast-feeding, such that after 6 months of daily nursing the concentration in milk and maternal body lipids is approximately 70% of the value at the time of delivery. These predictions were in good agreement with published values. Lastly, the investigators modeled the concentration of 2,3,7,8-TCDD in lipids or blood of a male subject for a time span of 60 years and compared it with literature values for German subjects. One of two curves constructed was computed assuming breast-feeding for the first

6 months of life followed by formula up to 1 year and the other considering feeding only formula for the same period of time. In both cases further nutrition was simulated to consist of the common diet. The predicted curves differed considerably during the first years of life. For the nonbreast-fed case, 2,3,7,8-TCDD concentrations decreased during the first year and subsequently increased, reaching a maximum at 16 years. For the breast-fed case, the simulation yielded a rapid rise of 2,3,7,8-TCDD in lipids followed by a 3-year decrease after weaning and merging at about 7 years with the concentrations of nonbreast-fed individuals. Subsequently, 2,3,7,8-TCDD concentrations leveled at between 2 and 3 ng 2,3,7,8-TCDD/kg body lipids until the end of life. The latter value was in agreement with average background levels for the German population. The half-life of nonmetabolic elimination (unchanged 2,3,7,8-TCDD) was calculated to be 0.42 years in newborns and 9.5 years in 40-year-old adults. The half-life of the fraction metabolized by the liver ranged from 1.5 years for newborns to approximately 10 years for a 40-year-old individual. The three times greater elimination half-life for the metabolized fraction relative to the nonmetabolized fraction in infants suggests that metabolic elimination does not play a major role in the elimination of 2,3,7,8-TCDD in infants. A key finding from the Kreuzer et al. (1997) study is the model prediction that the increased 2,3,7,8-TCDD burden observed as a result of breast-feeding does not lead to a raised lifetime value.

In rodents, placental transfer of CDDs to the fetus is relatively limited, but transfer during sensitive periods of organogenesis is biologically important as evidenced by effects on fetuses or offspring exposed *in utero*. Excretion into milk represents a major pathway for maternal elimination of CDDs and, therefore, for exposure to offspring. In C57BL/6N mice administered a single oral dose of 30 µg ^{14}C-2,3,7,8-TCDD/kg on Gd 11 the levels of 2,3,7,8-TCDD-derived radioactivity in the embryos on Gd 12, 13, or 14 were below 0.5% of the total 2,3,7,8-TCDD dose (Weber and Birnbaum 1985). In the dams, the highest concentration of radioactivity was in the liver (50–67% of total dose), whereas embryos had a relatively higher concentration of radioactivity in the heads than in the rest of the body. Approximately 0.03% of the administered dose was delivered to each embryo. In a different study in NMRI mice, pregnant females were administered a single dose of 25 µg ^{14}C-2,3,7,8-TCDD (oral, intraperitoneal, or subcutaneous) on Gd 16 and the distribution of radioactivity was examined in the pups on postnatal days 7–36 (Nau et al. 1986). At all times, the highest concentration of radioactivity in the pups (per gram of tissue) was found in the liver; extrahepatic tissues such as intestines and skin had a concentration of radioactivity that was approximately one order of magnitude lower than the liver. During the first postnatal week, 2,3,7,8-TCDD concentrations increased considerably in the pups. It was also found that during the first two weeks the pups received doses of 2,3,7,8-TCDD through milk which were, on a body weight basis, similar to those

which had been administered to their mothers prior to birth. In pups raised by untreated foster mothers, 2,3,7,8-TCDD tissue concentrations decreased rapidly due to organ growth with concomitant dilution of 2,3,7,8-TCDD. Abbott et al. (1996) examined the distribution of 2,3,7,8-TCDD in embryonic tissues of mice at times earlier than previous studies. Pregnant mice were treated with 2,3,7,8-TCDD on Gd 12 and embryonic tissues were examined at various times from 0.5 to 24 hours after dosing. The rate of accumulation of 2,3,7,8-TCDD reached a maximum in placental tissue in about 3 hours and, following a slight decline, remained relatively constant between 8 and 24 hours. After 24 hours, 0.27% of the maternal dose was detected in the placenta. In embryonic liver, 2,3,7,8-TCDD peaked approximately 8 hours after dosing and decreased thereafter, as opposed to maternal liver, where it remained constant after achieving an apparent maximum. The relative decrease in the rate of concentration in the embryonic liver was attributed to a rapid growth of the tissue during that time period. Distribution of 2,3,7,8-TCDD to embryonic palates followed a pattern similar to that in embryonic liver. Twenty-four hours after dosing, the secondary palates had 0.0045% of the administered maternal dose.

Van den Berg et al. (1987b) examined the transfer of CDDs and CDFs through the placenta and via the milk in Wistar rats. Prenatal exposure of the fetus was studied by administering a diet containing a fly ash extract from a municipal incinerator to rats from day 8 until 17 of pregnancy, after which time the rats were sacrificed. Postnatal transfer was assessed in rats fed the same diet during the first 10 days after delivery while nursing their offspring. Of the 49 tetra- to octa-CDDs, only 7 CDD congeners were detected and all had a 2,3,7,8-chlorine-substitution pattern. In the fetus, 2,3,7,8-TCDD had the highest retention (0.13% of total dose, 0.0092% of the dose/g). Retention decreased with the number of chlorine atoms; HpCDDs and OCDD were not detected. In the liver of offspring, 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, and the three 2,3,7,8-substituted HxCDDs had the highest retention (5.3–8.1% of total dose, 0.74–1.13% of dose/g). The 2,3,7,8-penta- and hexa-substituted congeners had the highest retention in the livers of pregnant and lactating rats (53.9–80.2% of total dose, 2.9–5.2% of dose/g). No significant differences were found in liver retention of tetra- to octa-chlorinated congeners between pregnant and lactating rats, but lactating females stored less CDDs in their adipose tissue. Similar results were reported by Li et al. (1995c) in Sprague-Dawley rats. These authors administered a single intravenous dose of 5.6 µg ^{14}C-2,3,7,8-TCDD/kg to pregnant rats on Gd 18. Sacrifices were conducted on Gd 19 and 20, and postnatal days 1 and 5. Groups of neonates were also cross-fostered between treated and nontreated dams to differentially assess transfer of 2,3,7,8-TCDD through the placenta and through nursing. Only about 0.01% of the dose administered to the dams was found in whole livers of fetuses one and two days after dosing (0.04 and 0.07% of dose/g fetal liver), indicating limited placental transfer. In contrast, the

concentration of 2,3,7,8-TCDD in the liver of neonates after 1 day of lactation was 0.65% of the administered dose/g liver, and this increased to 2.88% after 4 days of nursing. Four days after nursing, the liver concentration of 2,3,7,8-TCDD in neonates from dams dosed 1 day after parturition was 4.1% of the administered dose/g of liver, and this was higher than in the dam's liver (3.32%). As in earlier studies, the results from the cross-fostering experiments confirmed that nursing is a major pathway for transfer of 2,3,7,8-TCDD to the offspring.

The transfer of CDDs and CDFs via placenta and through milk was also investigated in a marmoset monkey administered a defined mixture of CDDs and CDFs subcutaneously 11 weeks prior to delivery (Hagenmaier et al. 1990). Concentrations of CDDs and CDFs were measured in a newborn 1 day after birth and in an infant of the same litter after a period of 33 days of lactation. The highest deposition in newborn liver was observed for 2,3,7,8-TCDD and 1,2,3,7,8-PCDD (54 and 51 pg/g wet weight, respectively) and corresponded to about 0.15% of the administered dose/g tissue. The concentration of all other congeners was <10% of the corresponding concentrations in adults. In contrast to liver, the concentrations of 2,3,7,8-substituted CDDs in newborn adipose tissue were at least one third the levels in adults, and for OCDD, the concentration in adipose tissue was three times higher that in adult adipose tissue. Transfer of CDDs through milk was considerable, though selective. The concentration of 2,3,7,8-TCDD and 1,2,3,7,8-PCDD in the infant's liver was 395 and 611 pg/g wet tissue, respectively; the corresponding concentrations in the mother's liver were 107 and 326 pg/g. However, the concentration of OCDD in infant's liver was less than 10% that of the mother's liver. Bowman et al. (1989b) examined the transfer of 2,3,7,8-TCDD from mother to offspring in rhesus monkeys. Female monkeys had been exposed to 2,3,7,8-TCDD for about 4 years to a diet (5 or 25 ppt) that provided an estimated 0.0001–0.0006 µg 2,3,7,8-TCDD/kg/day before breeding. Breeding started 10 months after exposure ceased. At weaning (4 months), the offspring had a concentration of 2,3,7,8-TCDD in mesenteric fat 4.3 times higher than in subcutaneous fat from their respective mothers. Bowman et al. (1989b) estimated that the mothers excreted between 17 and 44% of their 2,3,7,8-TCDD burden by lactation. Based on measurements of 2,3,7,8-TCDD in fat at 4, 12, and 24 months of age, it was found that in the young monkeys the decline in 2,3,7,8-TCDD in fat followed first-order, single-compartment kinetics with a half-life of approximately 181 days (Bowman et al. 1990). For the purpose of comparison, the mean half-life in 7 adult female rhesus monkeys was 391 days with standard error of 88 days (Bowman et al. 1989b).

In summary, CDDs can be transferred to the fetus across the placenta and, although the amounts may be relatively small, the transfer may have great biological significance if it occurs during critical periods of

organogenesis. Due to their lipophilicity, CDDs can concentrate in human breast milk and can be transferred to infants through nursing. In general, the amount of individual congeners in breast milk decreases as chlorination decreases. Excretion via milk is highest during the first weeks after delivery. Also, the concentration of CDDs in milk is higher in mothers breast-feeding their first child than in those breast-feeding their second child. CDDs transferred to infants through nursing are readily absorbed by the infants. A pharmacokinetic model predicted that the increased body burden in infants that results from breast-feeding does not translate into raised lifetime body burden. Studies in animals have also shown transfer of CDDs across the placenta and via mother's milk.

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

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-

specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

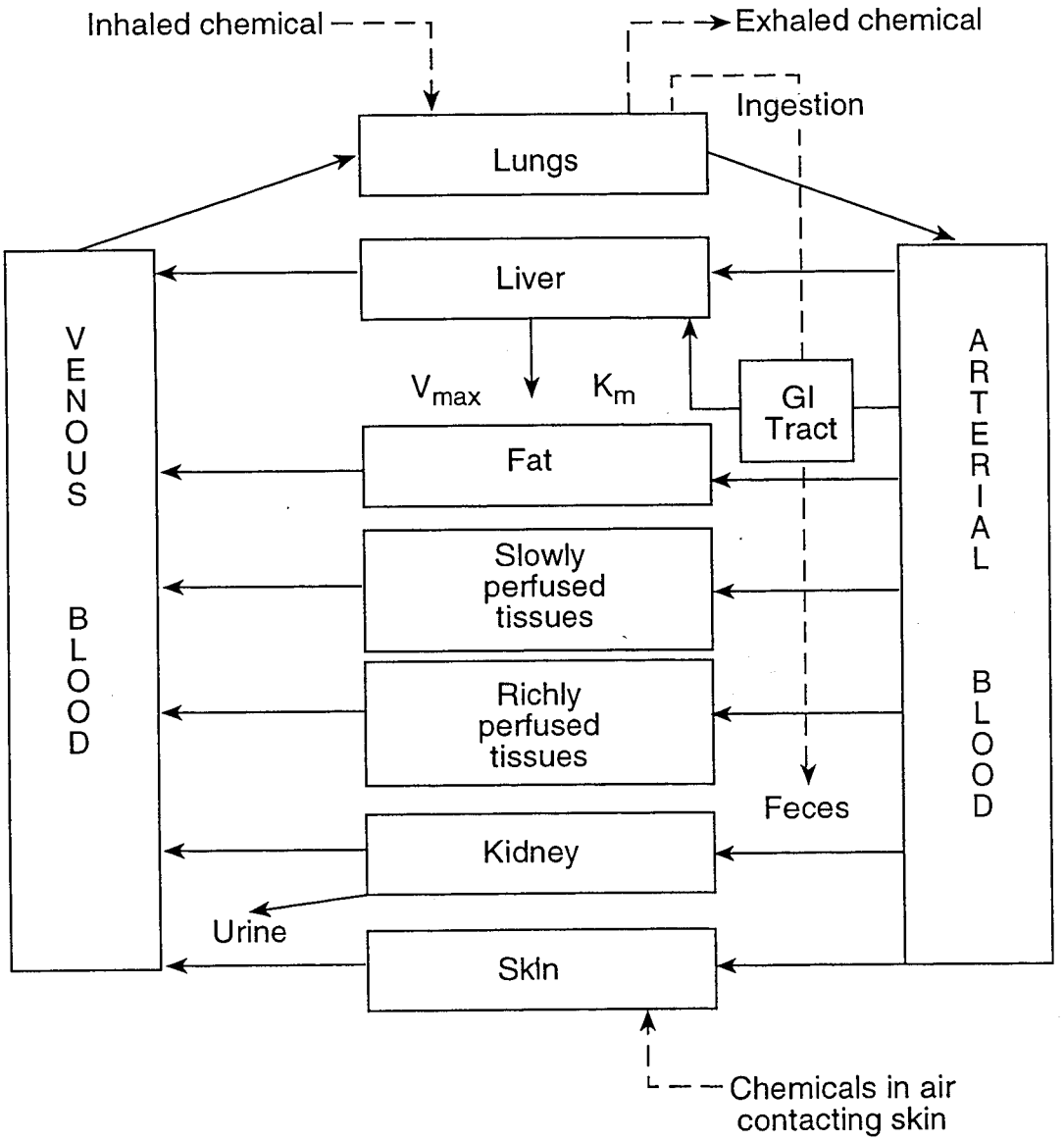
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many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

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

If PBPK models for CDDs 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.

PBPK models for 2,3,7,8-TCDD are discussed below. The pharmacokinetic behavior of 2,3,7,8-TCDD, especially distribution, has been shown to be dose-dependent and involves protein binding and enzyme induction in hepatic tissue. Thus, terms describing these interactions have been included in the animal models described below. Furthermore, since induction of these dioxin-binding proteins is a process mediated by the interaction of a dioxin-receptor (the Ah receptor) complex with specific binding sites on DNA additional terms were included in the models. For a detailed explanation regarding the Ah receptor and its involvement in the mechanism of action of 2,3,7,8-TCDD and structurally related halogenated aromatic hydrocarbons, see Section 2.4.2.

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



Source: adapted from Krishnan et al. 1994

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

2.3.5.1 Summary of PBPK Models.

The elimination of 2,3,7,8-TCDD from humans was evaluated using a PBPK model developed by Kissel and Robarge (1988). The steady-state adipose tissue concentration predicted by the model was similar to the lipid-based blood levels reported in the general population with no known special exposure to 2,3,7,8-TCDD. The model was also used to predict elimination of 2,3,7,8-TCDD from Ranch Hand Vietnam veterans. The predicted half-lives were similar to an experimental value based on analysis of 2,3,7,8-TCDD in blood of veterans with adipose burdens >10 ppt. The apparent half-lives increased as the adipose tissue concentration approached the steady-state level associated with background exposure. The model also predicted reasonably well the elimination of 2,3,7,8-TCDD from a volunteer who ingested a single 2,3,7,8-TCDD dose.

Leung et al. (1988) developed a five compartment PBPK model to describe the time course of 2,3,7,8-TCDD distribution in tissues of both the Ah-responsive C57BL/6J and Ah-less responsive DBA/2J mice (C57BL/6J mice respond to 2,3,7,8-TCDD with an increase in AHH activity, at a dose less than required to elicit this response in DBA/2J mice). The model also included binding in blood and two hepatic sites, one in the cytosol and the other in microsomes. It was found that the greater accumulation of 2,3,7,8-TCDD in the liver of C57BL/6J mice, relative to DBA/2J mice, was not attributed to the greater fat content in the DBA/2J mice, but to the more avid microsomal binding (CYP1A2) in the liver of the C57BL/6J mice. In the concentration range covered in the model simulations, the cytosolic receptor (Ah receptor) did not seem to play a major role in determining the overall tissue distribution pattern.

The same group of investigators (Leung et al. 1990b) developed a PBPK model to describe the tissue disposition of 2,3,7,8-TCDD in Sprague-Dawley rats. The description included the same compartments used in modeling the behavior of 2,3,7,8-TCDD in mice. The ratio of liver to fat concentration of 2,3,7,8-TCDD was found to be primarily determined by the dissociation constant of the microsomal binding protein (CYP1A2) and the basal and induced concentration of this protein in the liver. In general, there was agreement between the simulated data and experimental data from a single-dose study and a 7- and 13-week repeated-dosing study. However, the model underpredicted the concentration of 2,3,7,8-TCDD in the fat at low dose and overestimated the concentration at high dose for a 2-year feeding study. Induction of microsomal binding protein was necessary to account for the differences in disposition at low and high daily doses. Further refinements of Leung et al. (1988, 1990b) models were conducted by

Wang et al. (1997) and Santostefano et al. (1998) and included analyses of distribution and responses to 2,3,7,8-TCDD exposure at early times and in multiple tissues.

A receptor-mediated PBPK model was developed by Andersen et al. (1993). The model included interactions of the Ah-TCDD complex with DNA and was used to examine the tissue disposition of 2,3,7,8-TCDD and the induction of the dioxin-binding protein (presumably CYP1A2) and CYP1A1. It was found that tumor promotion correlated more closely with predicted induction of CYP1A1 than with induction of the hepatic binding proteins (CYP1A2, AhR). More recently, Andersen et al. (1997a, 1997b) developed a multicompartment geometric model of the liver that provided a better prediction of both total and regional induction of CYP450 proteins within the liver than conventional one-compartment models.

A mechanistic model (known as the NIEHS model) was constructed to describe 2,3,7,8-TCDD-mediated alterations in hepatic proteins in the rat (Kohn et al. 1993). This model included the tissue distribution of 2,3,7,8-TCDD and its effects on concentrations of CYP1A2 and CYP1A1 and the effects of 2,3,7,8-TCDD on the Ah, estrogen, and epidermal growth factor (EGF) receptors over a wide range of 2,3,7,8-TCDD doses. The model predictions were compared to experimental data from 2,3,7,8-TCDD promotion studies. The biochemical response curves for the proteins examined were hyperbolic, indicating a proportional relationship between target-tissue dose and protein concentration at low 2,3,7,8-TCDD doses. Also, the model successfully reproduced the observed tissue distribution of 2,3,7,8-TCDD, the concentration of CYP1A2 and CYP1A1, and the effects of 2,3,7,8-TCDD on the Ah, estrogen, and EGF receptors over a wide dose range.

Carrier et al. (1995a) developed a model that describes the distribution kinetics of 2,3,7,8-TCDD and related chemicals (with chlorine substitutions in positions 2,3,7, and 8) in various mammalian species, including humans. Their model takes into account cellular diffusion, binding of the chemicals with the Ah receptor and with proteins, and enzyme induction in the liver. The model was used to describe the distribution of CDDs between liver and adipose tissue as a function of overall body concentration. Model simulations showed that the fractions of the body burden contained in the liver and adipose tissue vary nonlinearly as a function of the overall body concentration; this was in agreement with published data in rodents, monkeys and humans. The authors further modeled the disposition kinetics of CDDs in liver, adipose tissue, and whole body as a function of time (Carrier et al. 1995b). The results showed that the rate of change in CDD tissue concentrations varies as a function of total body burden such that whole body

elimination rate decreases as body burden decreases, suggesting nonlinear disposition kinetics. This was also in agreement with published data on absorption and elimination kinetics of CDDs in rats and humans.

2.3.5.2 Comparison of PBPK Models for 2,3,7,8-TCDD.

Several models that describe the disposition of 2,3,7,8-TCDD in animals and one in humans were identified from the literature. In the Leung et al. (1988, 1990b) models in mice and rats, tissue 2,3,7,8-TCDD concentration ratios, particularly liver concentrations, were related both to intrinsic partitioning and to the presence of specific cytosolic and microsomal 2,3,7,8-TCDD-binding proteins. This is in contrast to other PBPK models developed for similar, persistent lipophilic chemicals, which distributed the chemicals between organs based on experimentally observed concentrations ratios under various dosing conditions. This could explain why two organs having the same partition coefficients contain very different 2,3,7,8-TCDD concentrations under a particular experimental condition. Carrier et al. (1995a, 1995b) developed a similar model, which also included other 2,3,7,8-substituted dioxins and furans and simulated experimental data on rodents, monkeys, and humans. The Andersen et al. (1993) model extended the Leung et al. (1988, 1990b) models by including induction of binding proteins/enzymes and of 2,3,7,8-TCDD metabolism in response to ternary interactions of 2,3,7,8-TCDD, the Ah receptor, and DNA binding sites and correlated various tissue dose measures with the promotional efficacy of 2,3,7,8-TCDD. The five-compartment liver model described by Andersen et al. (1997a, 1997b) provided a better description of mRNA production and regional localization of induced proteins, consistent with immunohistochemical information, than conventional one-compartment models. The model constructed by Kohn et al. (1993) suggested possible biochemical mechanisms which could explain a complex response to exposure to 2,3,7,8-TCDD such as cell proliferation in female rats. This model not only included enzyme induction and the Ah receptor, but also the estrogen and EGF receptors, all of which seem to be involved in a complex sequence of events that lead to cell proliferation as a result of 2,3,7,8-TCDD exposure. In contrast with the models developed for animals and described above, the Kissel and Robarge (1988) fugacity-based model for humans was used to predict vehicle-dependent uptake and elimination of 2,3,7,8-TCDD without including any Ah receptor-related terms. (Fugacity is defined as the “escaping tendency” of a substance in a phase.) Pharmacokinetic parameters used in the various models are listed in Table 2-7.

Table 2-7. Pharmacokinetic Parameters for 2,3,7,8-TCDD Used in PBPK Models

Parameters	C57BL/6J mouse[a]	DBA/2J mouse[a]	Sprague-Dawley rat[b]	Human[c]	Wistar rat[d]
Partition coefficient (tissue/blood)					
Liver	20	20	20	25	20
Fat	350	350	350	300	375
Rapidly perfused (kidney)	20	20	20	7–10	20
Slowly perfused (skin)	250	250	40	30	30
Slowly perfused (muscle)	250	250	40	4	30
Biochemical constants					
Binding capacity to hepatic cytosolic protein (nmol/liver)	0.0042	0.0042	0.054	–	0.0038
Binding affinity to hepatic cytosolic protein (nM)	0.29	2	0.015	–	0.035
Binding capacity to hepatic microsomal protein (nmol/liver)	20	20	–	–	–
Noninduced binding capacity to hepatic microsomal protein (nmol/liver)	–	–	25	–	10
Induced binding capacity to hepatic microsomal protein (µmol/liver)	–	–	175	–	85
Binding affinity to hepatic microsomal protein (nM)	20	75	7	–	6.5
First-order metabolic rate constant (per hour per kg liver)	3.25	1.75	2	–	1.65
Absorption constant from gastrointestinal tract into liver (per hour)	0.02	0.02	0.2	–	–
Binding to blood	2.5	2.5	2.5	–	–

[a] Leung et al. 1988
[b] Leung et al. 1990b
[c] Kissel and Robarge 1988
[d] Andersen et al. 1993

2.3.5.3 TCDD Models

The Kissel and Robarge Model

Description of the Model. The elimination of 2,3,7,8-TCDD from humans was described with a fugacity-based model using physiologically based parameters (Kissel and Robarge 1988). In this model, transport of 2,3,7,8-TCDD was assumed to be perfusion-limited (flow-limited) and 2,3,7,8-TCDD was assumed to be uniformly distributed within each tissue group or fluid phase, and tissue levels were considered to be in equilibrium with exiting fluids (blood, urine, bile). Because 2,3,7,8-TCDD appears to be poorly metabolized in humans, the model did not include terms for metabolites. Transport between gut lumen and gut tissue was described as a diffusive process. Included in the differential equations used to solve the system were data for several diets. Body compartment sizes and densities used in the simulations of background exposure and of elimination from individuals with body burdens similar to those of Ranch Hand veterans were based on reference-man data. Tissue perfusion rates and partition coefficients were obtained from the literature. The diet used in all simulations was adapted from the literature and also included a typical intake of added fats and oils. The fugacity capacity of the various diet components, gastric secretions, and fecal materials were either calculated or obtained from the literature. The model was used to predict tissue levels resulting from background exposures, elimination of 2,3,7,8-TCDD from Ranch Hand veterans, and elimination of 2,3,7,8-TCDD from a human volunteer.

Validation and Discussion. The steady-state adipose tissue concentrations predicted by the model, assuming no metabolism and a daily background exposure of 50 pg/day in North America, was 7.7 ppt. This value was similar to the lipid-based blood tissue levels reported in the general population with no known unusual exposure. The body burden projected for an intake of 100 pg/day fell outside the typical range associated with background sources. In simulating the elimination of 2,3,7,8-TCDD from Ranch Hand veterans the model assumed a background exposure of 50 pg/day and no metabolism. Under these conditions, apparent half-lives of 4.4, 5.2, 5.9, 7.2, 9.1, and 20 years were estimated for individuals with 2,3,7,8-TCDD adipose tissue concentrations of 100, 50, 30, 20, 15, and 10 ppt, respectively. This was in good agreement with a half-life of 7.1 years determined by analysis of blood lipids of veterans with adipose burdens >10 ppt (Pirkle et al. 1989). The results showed that the apparent half-lives increased greatly as tissue concentrations approached the steady-state level associated with background exposure. The model also approximated the uptake efficiency and elimination of 2,3,7,8-TCDD from a volunteer as reported by Poiger and Schlatter (1986). The fact that the predicted uptake efficiency was similar to that found

experimentally indicated that the estimated gut-lumen/gut-tissue mass transfer coefficient used was in the appropriate range. The reported half-life was 5.8 years and the model estimated a value of 6.7 years. Overall, the result suggested that a fugacity-based model can provide a viable method for describing overall elimination of 2,3,7,8-TCDD from humans, but it does not provide much insight regarding why elimination occurs in a particular manner.

The Leung et al. Model in Mice

Description of the Model. The model described by Leung et al. (1988) in mice provides quantitative descriptions of the time-course of elimination and levels of 2,3,7,8-TCDD in various organs of C57BL/6J mice and DBA/2J mice, a less responsive strain with higher body-fat content. The model contains five compartments: blood, liver, fat, richly perfused tissues, and slowly perfused tissues. To account for the 2,3,7,8-TCDD binding to receptor in the liver, the model contained two hepatic binding sites, one corresponding to the high affinity/low capacity cytosolic Ah receptor and the other to the inducible, low affinity/high capacity microsomal protein (CYP1A2). To simulate the intraperitoneal dose route used by Gasiewicz et al. (1983a), 2,3,7,8-TCDD was assumed to be absorbed into the liver compartment by a first-order uptake process. Bioavailability was assumed to be 100%. Partition coefficients, physiological parameters, and biochemical constants were obtained or calculated from the literature for each mouse strain. The kidney was assumed to be representative of the richly perfused tissue, whereas the slowly perfused tissue consisted mainly of muscle and skin. The binding capacity of the Ah-less responsive DBA/2J mice was set to equal that of the Ah-responsive mice even though the binding affinity is extremely low. Blood binding was described as a linear process with an effective equilibrium between bound and free 2,3,7,8-TCDD given by a constant. In blood, only one form of 2,3,7,8-TCDD is exchangeable in the tissues, which gives rise to kinetic behavior observed for diffusion-limited uptake into tissues.

Validation and Discussion. The simulation of the time-course of 2,3,7,8-TCDD concentration in the liver and fat of C57BL/6J mice after a single 10 μg/kg intraperitoneal injection generated by the model was in good agreement with the empirical data of Gasiewicz et al. (1983a). In trying to simulate the 3-times-higher liver/fat ratio of 2,3,7,8-TCDD in the C57BL/6L mice than in the DBA/2J mice, Leung et al. (1988) varied the fat content parameter in the C57BL/6J mice from 3 to 12% of body weight. The rationale was that the difference in hepatic concentration may have been due to greater capacity of the DBA/2J mouse to sequester the highly lipophilic 2,3,7,8-TCDD in adipose tissue. However, the results showed that 2,3,7,8-TCDD concentration in the liver was relatively insensitive to body fat content,

indicating that this was not an important factor influencing the disposition of 2,3,7,8-TCDD in the liver between the two strains of mice. The authors also found that the distribution of 2,3,7,8-TCDD was strongly influenced by the binding characteristics of the microsomal binding protein, especially the binding constant. The model gave good simulations of 2,3,7,8-TCDD excretion in both strains of mice. The simulation of the time-course of 2,3,7,8-TCDD concentration in the liver and fat of DBA/2J mice after a single 10 μg/kg intraperitoneal injection was not as good as that for the C57BL/6J mouse if the input was set to be consistent with the uptake and elimination. As with the C57BL/6J mouse, disposition of 2,3,7,8-TCDD in the liver of DBA/2J mice was greatly influenced by the microsomal protein binding constant and rather insensitive to changes in body fat content. The best fit of the empirical data was obtained with a binding constant of 75 nM (20 nM for the C57BL/6J mice), indicating that the 2,3,7,8-binding affinity to the hepatic microsomal protein in the DBA/2J mice was at least 3.5 times lower than that of the C57BL/6J mice.

The Leung et al. Model in Rats

Description of the model. This model in the Sprague-Dawley rat (Leung et al. 1990b) is an extension of the mouse model previously described and contains the same five compartments and two types of binding proteins: one corresponding to the high-affinity, low-capacity cytosolic 2,3,7,8-TCDD (Ah) receptor, and the other to the inducible, lower-affinity, high-capacity microsomal protein (CYP1A2). In the rat model, both types of binding proteins are defined with their own binding capacities and dissociation constants. The model was used to analyze experimental data for the single-dose studies of McConnell et al. (1984) and Rose et al. (1976), the 7-week Rose et al. (1976) study, the 13-week multiple-dose study of Kociba et al. (1978b), and the 2-year feeding study of Kociba et al. (1978a). In simulating the single-dose gavage study, 2,3,7,8-TCDD was assumed to be absorbed from the gastrointestinal tract by a first-order uptake process with a rate constant of 0.2/hour. In simulating the multidosing studies, bioavailability was assumed to be 100%. Physiological parameters, partition coefficients, and biochemical constants were calculated or obtained from the literature. Since there was no literature value for the binding capacity of the microsomal 2,3,7,8-TCDD-binding site in the rat, the value used was approximated by assuming it to be 10 times that of the mouse. The total microsomal binding capacity was apportioned between a basal level and an induced level. Also, AHH activity was taken to be the sum of a basal and induced level. A first-order metabolic rate constant for 2,3,7,8-TCDD metabolism in the liver was adjusted to provide a biological half-life of about 25–30 days.

Validation and Discussion. When the simulation of the McConnell et al. (1984) data for AHH induction included a term for induction of microsomal binding protein there was good agreement between the simulation and the empirical data. This had not been the case in an initial fitting which included a constant concentration of microsomal binding protein. Rose et al. (1976) examined the accumulation of 2,3,7,8-TCDD in adipose and liver tissues in rats administered 0.01, 0.1 and 1 µg 2,3,7,8-TCDD/kg/day 5 days a week for 7 weeks; sampling was done at weeks 1, 3, and 7. Model predictions of 2,3,7,8-TCDD concentrations were in good agreement with the experimental data except for concentration in fat at the 0.01 µg/kg/day dose level, in which case the model overpredicted the tissue concentration. Model formulations that had constant microsomal binding capacity overpredicted liver 2,3,7,8-TCDD concentrations at the lower-dose rates. Also, model formulations that contained final amounts of microsomal binding protein (CYP1A2) very different (much higher or lower) from the basal 200 nmol/liver could not simulate 2,3,7,8-TCDD concentration in liver at the highest-dose rate. Similar to the findings in mice, the liver/fat concentration ratio in rats was extremely sensitive to the dissociation constant of the microsomal binding protein. The model simulated well the data from the 7- and 13-week studies (Rose et al. 1976; Kociba 1978b), but not as well for data from the 2-year feeding study (Kociba et al. 1978a). There was underprediction of 2,3,7,8-TCDD concentration in fat and liver at the low dose (0.001 µg/kg/day) and overprediction of the liver concentration at the high-dose level (0.1 µg/kg/day). However, the ratios of the concentrations were consistent with those observed experimentally (1/1 at low doses, much higher in liver at high doses). According to Leung et al. (1990b), the underprediction at low dose may reflect the fact that the low-dose fat concentration in the 2-year study was close to the limit of detection and thus, subject to more error. At the high dose, physiological parameters such as tissue volume, metabolic constants, and amounts of binding proteins may have been altered by weight loss and changes in body composition, known effects of chronic exposure to 2,3,7,8-TCDD. Leung et al. (1990b) indicated that the overprediction at high dose could have been due to a loss of microsomal 2,3,7,8-TCDD-binding sites in the chronically exposed rats. The affinity of 2,3,7,8-TCDD for the microsomal binding protein appeared to be greater in the Sprague-Dawley rats than in C57BL/6J mice, which could account for the higher liver/fat concentration ratio in rats than in mice, assuming that the partitioning between tissues is approximately the same in the two species.

Wang et al. (1997) extended the work of Leung et al. (1988, 1990b) and Andersen et al. (1993) and developed an improved model to describe the disposition of 2,3,7,8-TCDD in multiple tissues from female Sprague-Dawley rats. The model of Wang et al. (1997) improved previous modeling attempts in some specific areas such as 1) providing information on distribution of 2,3,7,8-TCDD at early time points

(important for determining unique parameters related to mass transfer such as permeability), 2) better handling of mass balance when considering 2,3,7,8-TCDD binding to plasma proteins, and 3) improved estimation of physical and biochemical parameters. The Wang et al. (1997) model accurately described the time course distribution of 2,3,7,8-TCDD following a single oral dose, as well as the concentration of 2,3,7,8-TCDD in eight target tissues on day 3 after six different doses. The model described by Wang et al. (1997) was recently coupled to a biologically-based pharmacodynamic (BBPD) model to quantitatively describe the relationship between disposition and response in multiple tissues (Santostefano et al. 1998). This later model incorporated both pharmacokinetic and pharmacodynamic events to account for the ability to 2,3,7,8-TCDD to induce CYP1A1 and the fact that CYP1A2 is responsible for maintaining high concentrations of 2,3,7,8-TCDD in the liver. The results showed that the BBPD model accurately described the time course of CYP1A1 protein expression and EROD activity in the liver, skin, and kidneys. It also confirmed that EROD activity can be an appropriate marker for CYP1A1 protein expression, and the shape of the induction curves supported the hypothesis that similar time-dependent mechanism of 2,3,7,8-TCDD-induced CYP1A1 protein expression and associated EROD activity occurs in multiple tissues. This, in turn, suggested that parameter estimation in the study accurately described the Ah receptor-mediated mechanism on protein expression and enzymatic activities in multiple tissues.

The Andersen et al. Model

Description of the Model. This model (Andersen et al. 1993) is an extension of the earlier PBPK models developed by Leung et al. (1988, 1990b) for 2,3,7,8-TCDD. Like the earlier models, this model consists of five compartments. Each of the four tissue compartments has a specified blood flow, tissue compartment volume, and a tissue blood volume. Movement of chemical from blood to tissue was modeled to be proportional to the product of a permeation coefficient times surface area for the tissue. When this product is lower that the specified blood flow for the tissue, tissue uptake is diffusion-limited. Because of the diffusion-limited tissue compartments, the model did not require blood binding to match the time-course of tissue uptake. It was assumed that in the liver both the Ah receptor and the inducible binding protein act to sequester 2,3,7,8-TCDD through a capacity-limited binding process, and the binding protein was assumed to be CYP1A2. Binding interactions with CYP1A2 and CYP1A1 were described by reversible equilibrium relationships, which is valid as long as the rate constants for association/dissociation are large. It was also assumed that the DNA sites to which the Ah-2,3,7,8-TCDD complex binds are present at much lower concentrations than the Ah-ligand complex. For both CYP1A1 and CYP1A2 induction, it was assumed that the Ah-ligand complex formation was equivalent, but that the Hill term, *n*, (a measure of

interaction for multiple Ah-ligand complex binding sites) and the Hill binding constant were different for the two responses. The model also allowed for autoinduction of metabolism following 2,3,7,8-TCDD treatment. Data from Abraham et al. (1988) and Krowke et al. (1989) were analyzed. The former study provided dose-response characterization of concentrations of 2,3,7,8-TCDD in liver and of liver CYP1A1 activity and time-course characterization of 2,3,7,8-TCDD concentration in tissues and enzyme activities in female Wistar rats. Krowke et al. (1989) examined liver and fat concentrations in male Wistar rats dosed weekly for up to 6 months. In addition, Andersen et al. (1993) examined the potential correlation between several measures of dose estimated by the model and the promotional efficacy and carcinogenicity of 2,3,7,8-TCDD in Sprague-Dawley rats. Cancer data from Kociba et al. (1978a) and Pitot et al. (1980) were analyzed.

Validation and Discussion. Abraham et al. (1988) found that the disposition of 2,3,7,8-TCDD in liver and fat from rats administered a single subcutaneous dose (0.001–10 μg/kg) of the chemical was highly dose-dependent. The disproportionately higher concentration in the liver at higher doses appeared to be due to induction of a dioxin-binding protein, presumably CYP1A2. The model developed by Andersen et al. (1993) successfully simulated the experimental data. The affinity of the binding protein was estimated to be 6.5 nmol, while a value of 1 for *n* suggested little interaction among 2,3,7,8-TCDD-responsive DNA-binding sites involved in the expression of CYP1A2. For describing induction of CYP1A1, an *n* of 2.3 was required, which suggested possible interactions among DNA-binding sites for the Ah-ligand complex with this gene. The simulation of the time-course of elimination from liver and of induction of CYP1A1 was in good agreement with the empirical data, but required the inclusion of time-dependent growth parameters over the 100 days of the experiment. The model also successfully simulated the data from the repeated-dosing study by Krowke et al. (1989) after small adjustments were made to fat and slowly perfused tissue parameters. The measures of dose that were used for comparison with the promotional and carcinogenic properties of 2,3,7,8-TCDD were integrated total liver concentration during the treatment period, or integrated free liver 2,3,7,8-TCDD concentration. Also, measures of tissue dose related to enhanced expression of CYP1A1 and hepatic binding proteins were calculated and examined for correlation with promotional activity. Results of the analysis revealed that under the exposure conditions, the tumor promotional response of 2,3,7,8-TCDD in the rat liver most closely correlated with integrated expression of the CYP1A1 gene. However, Andersen et al. (1993) indicate that since there is no expectation of causality between tumor responses and induction of CYP1A1 (or CYP1A2), the correlation should be regarded cautiously. Consistent with the findings of Leung et al. (1988, 1990b), the results from

the Andersen et al. (1993) study showed that over a certain dose range (e.g., at doses several fold above background), protein (CYP1A2) induction greatly alters 2,3,7,8-TCDD disposition.

Recently, Andersen and co-workers developed a model of hepatic enzyme zonation that was combined with the PBPK model of protein induction (Andersen et al. 1993) to create a multicompartmental representation of the liver architecture that can be used to predict the degree of induction in both the whole liver and in specific regions (Andersen et al. 1997a, 1997b). A geometric representation was used to divide functional units (based on enzyme distribution) within the liver into five zones. The primary objective was to compare model predictions for regional induction with regional protein induction as visualized by immuno-histochemistry. The data set modeled included analysis of tissue distribution of 2,3,7,8-TCDD in the first days or weeks after a single dose, time course studies for about 100 days after a single dose, and initiation-promotion studies in rats dosed for up to 6 months. The results showed that the five-compartment model was more successful than conventional homogeneous one-compartment liver models not only in simulating low-dose behavior for mRNA in whole liver but also in representing immunohistochemical observations. Five or more compartments were required to give a sharp boundary between induced and noninduced regions of the liver. When the five-compartment liver model was used to account for CYP1A1 and CYP1A2 induction and regional distribution of induced enzymes, the low-dose behavior appeared to be nonlinear and was better described, with a large *n* value (Hill coefficient) and a range of affinities in the liver covering about 81-fold differences between centrilobular and periportal regions.

The Kohn et al. (NIEHS) Model

Description of the Model. Kohn et al. (1993) constructed a mathematical model (the NIEHS model) to describe 2,3,7,8-TCDD tissue distribution and 2,3,7,8-TCDD-mediated alterations in hepatic proteins in the rat. The model assumed that 2,3,7,8-TCDD mediates increases in liver concentration of transforming growth factor-α (TGF-α) by a mechanism which requires the Ah receptor. TGF-α subsequently binds to the EGF receptor, a process which is known to cause internalization of the receptor in hepatocytes. This is thought to be an early event in the generation of a mitogenic signal. The model included equations for the Ah receptor-dependent induction of CYP1A1 and CYP1A2 activity and of the Ah receptor itself. Because it was also assumed that estrogen action is required for 2,3,7,8-TCDD-mediated induction of TGF-α, production of the estrogen receptor, CYP1A2-catalyzed formation of catechol estrogens, and deactivation of estrogens by glucuronidation were included in the model. The model predictions were compared to the two-stage initiation-promotion data of Tritscher et al. (1992) and Sewall et al. (1993). Gavage doses

equivalent to 3.5–125 ng 2,3,7,8-TCDD/kg/day for 30 weeks were used in these studies. Data from Abraham et al. (1988) were also analyzed. Model parameters were obtained from the literature or calculated from experimental data and adjusted to make the model reproduce the observations of Tritscher et al. (1992) and Sewall et al. (1993).

Validation and Discussion. The model prediction for the percentage of absorption (>90%) from ingestion of 2,3,7,8-TCDD was in good agreement with experimental data of Rose et al. (1976). The model also predicted that 92.2% of the metabolite appears in the feces and 7.8% in the urine at a dose of 125 ng/kg/day. The dose of 2,3,7,8-TCDD did not have a significant effect on these predictions. From the fit to the data of Abraham et al. (1988), the model predicted an initial and overall half-time clearance from liver of 11.8 and 13.5 days, respectively, which is very close to the experimentally obtained 11.5 and 13.6 days. Similar good agreement was obtained for half-time elimination from fat (22.3 days versus 24.5 days). The model predicted a linear relationship between administered dose and the concentration of 2,3,7,8-TCDD in the liver at doses between 3.5 and 125 ng/kg/day, which was in good agreement with the data of Tritscher et al. (1992). The relationship between 2,3,7,8-TCDD dose and induction of both CYP1A1 and CY1A2 was best fit by an hyperbolic curve suggesting lack of cooperative interactions among binding sites. The hyperbolic curve was consistent with the experimental data for induction of these proteins from Tritscher et al. (1992). The model also predicted that the fractional occupancy of the Ah receptor by 2,3,7,8-TCDD rises from 13.4% at a dose of 3.5 ng/kg/day to 69.3% at 125 ng/kg/day. The model prediction of the degree of internalization of the EGF receptor as a function of the concentration of TGF-α was also hyperbolic in shape and successfully reproduced the experimental data of Sewall et al. (1993). Kohn et al. (1993) indicate that as this response may be involved in the mechanism of tumorigenesis in 2,3,7,8-TCDD-treated rats, it would be expected that it would correlate with tumor incidence better than does tissue dose. If so, extrapolation of effects at high dose to low doses may underestimate low-dose effects. However, extrapolation from low dose to extremely low dose would still be valid. The model predicted that 10 days after administration of a single dose of 1 μg 2,3,7,8-TCDD/kg there should be a greater decrease in plasma membrane EGF receptor in female rat liver than in male rat liver, which is consistent with the observed lower sensitivity of the male. Consistent with the experimental data, the model reproduced the decrease in hepatic estrogen receptor (ER) level resulting from exposure to 2,3,7,8-TCDD, and the relationship between concentration of 2,3,7,8-TCDD and amount of receptor was also hyperbolic. Overall, the model's success in reproducing the observed responses to 2,3,7,8-TCDD for the various proteins included in the model supports the proposed mechanism that internalization of the EGF

receptor in response to induction of TGF-α may be the origin of the mitogenic signal important for carcinogenesis.

The Carrier Model

Description of the Model. The first part of this model provides a quantitative description of the distribution of 2,3,7,8-substituted CDDs (and CDD-like compounds) between liver and adipose tissues as a function of overall body concentration at any given time (Carrier et al. 1995a). In a second step, differential equations were used to describe the disposition of CDDs in liver, adipose tissues, and whole body as a function of time (Carrier et al. 1995b). The first step of the model was based on several hypotheses: 1) changes in overall CDD concentration are slow relative to intertissue diffusion exchanges, protein induction, and binding of CDDs in the liver; 2) CDDs are mainly in adipose tissue and in the liver, but exchanges between these two sites are mediated via the blood; 3) the liver synthesizes proteins that bind free CDDs according to standard mass action association-dissociation mechanisms; 4) synthesis of binding proteins in the liver is linked to binding of free CDDs to the Ah receptor; 5) CDDs in fat deposits within the liver contribute to the overall liver burden and is taken into account; and 6) small amounts of CDDs are contained in organs other than the liver and adipose tissues and this fraction is assumed to be constant. In the second step, CDDs were assumed to be eliminated mainly by hepatic clearance; elimination by lactation or transplacental distribution was not considered. Model simulations of various experimental data sets, as specified below, were conducted. When not readily available, anatomical and physicochemical parameters were obtained from laboratory or clinical data.

Validation and Discussion. The model successfully simulated data from Abraham et al. (1988), who provided dose-response characterization of concentrations of 2,3,7,8-TCDD in the liver of rats after a single dose of the compound. Analysis of the data showed that the higher the body burden, the higher the proportion of the burden contained in the liver. However, the model predicted that a plateau is reached when body burden is >1 mg 2,3,7,8-TCDD/kg body weight. The model predictions were also in good agreement with experimental data from Van den Berg et al. (1986a), who administered a single dose of a mixture of CDDs and CDFs to rats and hamsters and with data in monkeys administered a single oral dose of 2,3,7,8-TCDD (McNulty et al. 1982). Results from simulations conducted on data from chronic studies in rats (Kociba et al. 1978a; Rose et al. 1976) and on human data from Yusho patients also showed that increasing the body burden results in an increase in the fraction of the body burden present in the liver and in an increase in the liver/adipose concentration ratio. These changes in fractional distributions were

attributed to the affinity of specific liver proteins for binding of free hepatic CDDs and the saturable capacity of the binding proteins at high concentration of free CDDs. Model simulations of elimination data in rats after single (Abraham et al. 1988) or repeated doses (Kociba et al. 1978a; Rose et al. 1976) of 2,3,7,8-TCDD, as well as data from a Yu-Cheng patient agreed well with the empirical data and showed that disposition kinetics of 2,3,7,8-substituted CDDs are nonlinear (i.e., as body burden decreases with time, liver and adipose tissue half-lives increase). According to the model, an additional factor that can influence the disposition kinetics of 2,3,7,8-CDDs is a rapid change in body weight and/or adipose tissue mass. A rapid loss of adipose tissue whether by dieting or in patients experiencing anorexia, would result in a higher concentration of the chemical in the remaining adipose tissue, particularly if the loss of tissue is much faster than whole body elimination via the liver.

2.3.5.4 Risk Assessment.

In early efforts to model the disposition of persistent halogenated aromatic hydrocarbons, disposition was described by simple partitioning between the blood and the various tissues with first-order metabolism in the liver. In those studies, the role that extensive tissue binding to particular cellular proteins might play in determining the overall disposition of the chemical was not accounted for. In contrast, the descriptions of Leung et al. (1988, 1990b) and Carrier et al. (1995a, 1995b) attempted to provide a biochemical basis for the observed tissue distribution. The use of this type of model may help explain interspecies differences in 2,3,7,8-TCDD sensitivity and carcinogenicity. The rodent PBPK model for 2,3,7,8-TCDD revealed very consistent behavior between species, and some of the predictions of high dose-low dose behavior were verified.

One advantage of a description that explicitly includes protein binding is the ultimate ability to develop pharmacodynamic models for 2,3,7,8-TCDD (and related chemicals) toxicity based on Ah receptor occupancy or Ah-TCDD complex concentration *in vivo* and to realistically couple it with the biologically based cancer models (or with models for other 2,3,7,8-TCDD responses). This was attempted by Andersen et al. (1993) and Kohn et al. (1993), who included estimates of binding constants between the Ah receptor and 2,3,7,8-TCDD and between the Ah receptor-dioxin complex and sites on DNA. Santostefano et al. (1998) extended previous modeling attempts by determining parameter values based on time course of CYP1A1 and CYP1A2 responses in multiple tissues using a simultaneous PBPK and BBPD models. However, as noted by Andersen et al. (1993), in order to develop a complete biologically motivated risk-assessment model, these dosimetry models need to be combined with quantitative descriptions of cell and

tissue responses. Kohn et al. (1993) used the NIEHS model to successfully predict tissue concentrations of 2,3,7,8-TCDD and of various induced proteins involved in the carcinogenic response to 2,3,7,8-TCDD and suggested that such a model might permit extrapolation of responses beyond the range obtained from experimental data and lead to scientifically sound approaches for estimating risks of adverse health effects of exposure to 2,3,7,8-TCDD. The importance of the results of Kohn et al. (1993) can be illustrated by the finding that the dose-response curves for various proteins were hyperbolic rather than sigmoid. Sigmoidicity in the response requires a higher concentration to produce a given response at low dose than does a hyperbolic response having the same concentration for half-maximal effect. This implies that the response is approximately linear at very low doses.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

The mechanism of absorption of CDDs by the inhalation and dermal routes of exposure is not known. Transfer of CDDs from the aqueous environment of the intestine across cell membranes is predominantly limited by molecular size and lipid solubility. The overall evidence indicates that 2,3,7,8-substituted tetra- and pentachlorinated congeners are well absorbed. In contrast, OCDD was poorly absorbed from the gastrointestinal tract of rats (Birnbaum and Couture 1988), but absorbed more on chronic exposure (Birnbaum et al. 1989a). Absorption is also vehicle-dependent (Poiger and Schlatter 1980). Highly chlorinated congeners, although absorbed in small amounts, can accumulate in the liver. Results from studies in thoracic duct-cannulated rats showed that 2,3,7,8-TCDD was transported primarily via the lymphatic route and was predominantly associated with chylomicrons (Lakshmanan et al. 1986). Several studies have examined the distribution of CDDs between blood and adipose tissue. Patterson et al. (1989d) showed that on a lipid basis the serum/adipose ratio for 2,3,7,8-TCDD in humans was approximately 1:1, and this correlation held over a concentration range of almost three orders of magnitude. They also found that in blood <10% of 2,3,7,8-TCDD was associated with red blood cells, which according to Patterson et al. (1989d), suggested that most of 2,3,7,8-TCDD in blood was bound to serum lipids and lipoproteins. However, the distribution between plasma lipid and adipose tissue increased with chlorine substitution, which indicated that higher chlorinated congeners have a higher binding affinity for plasma proteins (Patterson et al. 1989d; Schecter et al. 1990). Experiments of *in vivo* binding of CDD congeners to various serum fractions revealed that as chlorine content increased, binding to lipoproteins gradually decreased, 75% of 2,3,7,8-TCDD was found bound to lipoprotein compared to 45% for OCDD (Patterson et al.

1989b). However, binding to other proteins increased with chlorine content (20% for 2,3,7,8-TCDD versus 50% for OCDD). Also, fewer CDDs (<10%) were bound to the chylomicrons in serum. In studies *in vitro* with human whole blood, 80% of the applied amount of 2,3,7,8-TCDD was associated with lipoproteins, 15% with proteins, and 5% with cellular components (Henderson et al. 1988). Also, there is some evidence that 2,3,7,8-TCDD and related stereoisomers may be associated with plasma prealbumin (McKinney et al. 1985a; Pedersen et al. 1986). Within the lipoprotein fraction and per mole of lipoprotein, 2,3,7,8-TCDD has highest affinity for very low density lipoprotein (VLDL), followed by LDL and HDL (Marinovich et al. 1983). A study using cultured human fibroblasts presented some evidence that specific binding to LDL and the LDL receptor pathway may explain in part the rapid early uptake of 2,3,7,8-TCDD with LDL entry (Weisiger et al. 1981).

2,3,7,8-substituted CDDs are the predominant congeners retained in tissue and body fluids from rodents and monkeys (Abraham et al. 1989b; Van den Berg et al. 1983), although minor retention of non-2,3,7,8-substituted congeners has been reported in the rat (Abraham et al. 1989b). In general, the tissue distribution of CDDs is congener-specific and depends on the dose and route of administration (see Van den Berg et al. 1994 for review). In rats, for any particular organ or tissue, distribution within 24 hours of dosing depends on blood perfusion rate and relative tissue size, such that relatively high initial CDD concentrations are found in the adrenal glands and skeletal muscle (Pohjanvirta et al. 1990). Shortly thereafter, the liver and adipose tissue become the major storage sites (Allen et al. 1975; Lakshmanan et al. 1986; Rose et al. 1976). Data from studies in humans, marmoset monkeys and rats suggest that the distribution ratio between liver and adipose tissue increases with increasing degree of chlorination (Abraham et al. 1989c; Neubert et al. 1990a; Thoma et al. 1990), but also depends on the dose, metabolic rate, route of administration, and the time of observation after dosing. In non-human primates and in humans, the liver appears to be a less significant storage site than in rodents (Van Miller et al. 1976). In mice, the Ah receptor does not appear to play a significant role in 2,3,7,8-TCDD body distribution for adipose tissue, skin, kidney, and total-body concentration (Birnbaum 1986). However, it plays some role in liver retention (Birnbaum 1986; Gasiewicz et al. 1983a) and this was found to be related to inducibility of cytochrome P-450 (Leung et al. 1988), in particular CYP1A2. Distribution of 2,3,7,8-TCDD in mice has been shown to be age-dependent (Pegram et al. 1995). The greater fat content of some tissues in old mice enhances partitioning of 2,3,7,8-TCDD into the tissues, while decreased perfusion prolongs clearance (Pegram et al. 1995). Some acute- and chronic-duration studies in rats have demonstrated a disproportionate dose-dependent distribution of 2,3,7,8-TCDD in liver and adipose tissue (Abraham et al. 1988; Kociba et al. 1978b). The greater the dose, the greater the liver/adipose tissue ratio. A disproportionate

dose-dependent distribution has also been demonstrated in mice (Diliberto et al. 1995). 2,3,7,8-TCDD-derived radioactivity in the liver was found associated preferentially with the microsomal fraction (Allen et al. 1975). Information summarized by Van den Berg et al. (1994) suggests that the disproportionately greater hepatic concentration of 2,3,7,8-TCDD after exposure to higher doses may be explained in part by the induction of a hepatic-binding species, CYP1A2. This distribution parameter is also explained by the Carrier et al. (1995a,b) model in humans.

There is some experimental data to suggest that the fetal/neonatal period may be more sensitive to the toxicity of CDDs than the adult animal. Several studies have shown that limited placental transfer of CDDs takes place in rodents (Li et al. 1995c; Nau et al. 1986; Van den Berg et al. 1987b; Weber and Birnbaum 1985) and in humans (Schecter et al. 1996a). However, little is known about the mechanisms responsible for the transfer of CDDs across the placenta, the dependence of these mechanisms on the gestational period, and the distribution of these compounds in fetal tissue. However, CDDs and related chemicals are able to concentrate in breast milk, and limited human (Abraham et al. 1994; McLachlan 1993; Pluim et al. 1993b) and animal (Nau et al. 1986) data have indicated considerable absorption of these compounds by the nursing infant. Thus, while the *in utero* exposure of fetal tissues to CDDs may represent only a small percentage of the maternal body burden of CDDs, the breast-fed infants will receive a higher daily dose per body weight than adults. Further information regarding placental transfer and elimination of CDDs through breast milk is presented in Section 2.3.4.4.

As mentioned in Section 2.3.3, metabolic transformation of CDDs *in vivo* includes oxidation and reductive dechlorination as well as glutathione conjugation. Studies in two rat strains which differ greatly in sensitivity to 2,3,7,8-TCDD did not provide evidence for a role of toxicokinetics and metabolism in the difference in sensitivity (Pohjanvirta et al. 1990). Also, studies in various mice strains showed no significant Ah receptor-related differences in metabolic pathways (Gasiewicz et al. 1983a). While *in vitro* studies have shown similarities between most species regarding metabolite profile, the rate of 2,3,7,8-TCDD metabolism and the number of metabolites were reduced in hepatocytes in suspension culture from guinea pigs, a highly sensitive species (Wroblewski and Olson 1985). The overall evidence suggests that 2,3,7,8-TCDD can induce its own metabolism *in vivo*, but only at doses that could cause overt signs of toxicity (Van den Berg et al. 1994). It is important to consider the possibility of autoinduction at high doses because data obtained with exposure levels associated with a significant induction of CYP1A1 and CYP1A2 may not necessarily reflect toxicokinetic behavior at low-exposure levels.

Elimination of 2,3,7,8-substituted CDDs occurs mainly via the bile and the feces as polar metabolites; much smaller amounts are excreted via the urine. Moreover, in almost all mammalian species studied, the 2,3,7,8-TCDD-derived radioactivity in tissues is associated with the parent compound, suggesting that the hydroxylated and/or conjugated metabolites are rapidly eliminated from the body. Studies in mice showed that a strain of mice having a low affinity Ah receptor eliminate 2,3,7,8-TCDD at a much slower rate than mice with an Ah receptor of high affinity for the ligand (Gasiewicz et al. 1983a). These strain differences in body distribution and elimination could be explained not only by the differences in adipose tissue content, but also by the presence of a hepatic microsomal binding protein (Leung et al. 1988). Further studies in congenic mice suggested that the distribution and excretion of 2,3,7,8-TCDD is controlled primarily by the total genetic background and not by the allele present at the Ah-locus (Birnbaum 1986). Guinea pigs eliminate 2,3,7,8-TCDD considerably slower than other rodents (Olson 1986). This may reflect the relatively limited ability of the guinea pig to metabolize 2,3,7,8-TCDD and may contribute to the greater persistence and greater acute toxicity of 2,3,7,8-TCDD in this species. Results from a repeated-dosing study in rats showed that the rate-constant defining the approach to steady-state concentrations was independent of the dose over the range tested (Rose et al. 1976). This was consistent with evidence suggesting that autoinduction of 2,3,7,8-TCDD metabolism does not occur following exposure to sublethal doses. Autoinduction of metabolism could explain cases of dose-related excretion in which longer half-lives for elimination are seen at lower-exposure levels which are not associated with enzyme induction.

2.4.2 Mechanisms of Toxicity

The mechanism(s) of toxicity for CDDs is not completely understood but has been extensively studied, particularly for 2,3,7,8-TCDD, and numerous reviews are available on this subject (Birnbaum 1994a; Goldstein and Safe 1989; Kerkvliet 1995; Landers and Bunce 1991; Okey et al. 1994; Poland and Knutson 1982; Safe 1986, 1990; Silbergeld and Gasiewicz 1989; Whitlock 1987, 1993). Many CDDs, CDFs, coplanar PCBs, and other structurally related halogenated aromatic hydrocarbons are believed to share a common mechanism of action intimately related to similarities in their structural configuration. Most of what is known regarding the mechanism of action of these compounds is based on research in three main areas: structure-activity relationships for receptor binding and induction of a variety of biochemical and toxicological responses; genetic studies using inbred mouse strains; and studies at the molecular level which have elucidated key events in the actions of the receptor. Most of the studies providing this information used parenteral routes of exposure and/or *in vitro* tests systems. It is beyond the scope of this profile to discuss these studies in detail.

The extraordinary potency of 2,3,7,8-TCDD in evoking a dose-related induction of cytochrome P-450-associated AHH activity, the stereospecificity among related halogenated aromatic compounds to evoke this response, and the tissue specificity of enzyme induction, led Poland and Glover (1973b) to postulate the existence of an induction receptor. This receptor, the Ah receptor (Ah for aromatic hydrocarbon), was later identified in the cytosol of mouse liver cells (Poland et al. 1976) and, subsequently, in hepatic and extrahepatic tissues of a variety of laboratory animals, mammalian cell cultures, human organs and cell cultures, and also nonmammalian species (Okey et al. 1994). Results from structure-binding relationships for a series of CDD congeners using mouse hepatic cytosol showed that not all the congeners had the same affinity for the Ah receptor; affinity was found to be determined by the chlorine-substitution pattern (Mason et al. 1986; Poland et al. 1976, 1979). The most active compound was 2,3,7,8-TCDD, which is substituted in all four lateral positions. Addition of one, two, or four nonlateral chlorine substituents, or removal of lateral chlorine substituents, resulted in congeners with lower binding affinities. The stereospecific nature of the binding suggested the existence of a cytosolic receptor as a mediator in responses caused by 2,3,7,8-TCDD and related compounds.

2,3,7,8-TCDD and structurally related halogenated aromatic compounds induce a variety of microsomal enzymes primarily in the liver. The most widely studied of these responses are induction of hepatic AHH and EROD (markers of CYP1A1 activity) in mammalian cell cultures and in laboratory rodents (Goldstein and Safe 1989; Poland and Glover 1973a; Safe 1986, 1990). Several studies have examined the *in vitro* and *in vivo* structure-activity relationships for CDDs as inducers of hepatic and extrahepatic CYP1A1 activity (Bradlaw and Casterline 1979; Harris et al. 1990; Mason et al. 1986; Poland and Glover 1973a; Poland and Knutson 1982; Poland et al. 1979). The most active CDDs were substituted in their 2,3,7, and 8 positions, and the structure-activity relationships for induction and receptor binding assay were comparable. The molecular dimensions of the binding site was initially estimated to fit ligands that were approximately 3×10Å (Poland and Knutson 1982), which would accommodate molecules such as 2,3,7,8-TCDD; however, approximate dimensions of 12x14x5Å would be required to accommodate other chemicals (e.g., 3-MC or β-naphthoflavone), known to bind (Landers and Bunce 1991; Rannug et al. 1991; Waller and McKinney 1995). Although results from these experiments provided further evidence for a receptor-mediated mechanism of action, there was not strictly a linear correlation between Ah receptor binding and enzyme induction. Mason et al. (1986) suggested that a number of factors, including differential solubilities of the CDDs in the assay buffer system at higher concentrations, may contribute to the nonlinearity. They also suggested that structure-dependent receptor protein-ligand interactions which occur after the initial binding event may have played a role in the nonlinearity of the data sets.

Furthermore, differential rates of metabolism and elimination of particular CDDs also likely account for the comparative differences between studies *in vivo* and *in vitro* (Birnbaum 1985).

Numerous studies have examined the structure-toxicity relationships for CDDs. For example, examination of lethality data in guinea pigs revealed that the fully lateral-substituted tetra- to hexachloro-substituted isomers were the most toxic congeners, and the structure-activity relationships were comparable to those observed for their AHH-induction and receptor-binding activities (Eadon et al. 1986). Similar results have been reported for responses such as body weight loss and thymic atrophy (Mason et al. 1986; Safe 1987). Furthermore, there was an excellent correlation between the *in vitro* AHH induction potencies and the *in vivo* responses. Additional end points for which structure-toxicity relationships correlate well with structure-induction potencies and/or Ah receptor-binding affinities are epidermal responses such as the keratinization of the mouse teratoma XB cells and the production of skin lesions in genetically inbred haired and hairless mice (Knutson and Poland 1980, 1982), suppression of the splenic antibody response to SRBC (Kerkvliet et al. 1985), antiestrogenicity (Gierthy et al. 1987; Krishnan and Safe 1993), and teratogenicity (Weber et al. 1985). Taken together, these results, and others, strongly supported the role of the Ah receptor in mediating the toxicity of 2,3,7,8-TCDD and related halogenated aromatic hydrocarbons.

As previously mentioned, 2,3,7,8-TCDD and structurally related compounds induce a wide range of biological responses, including alterations in metabolic pathways, body weight loss, thymic atrophy, impaired immune responses, hepatotoxicity, chloracne and related skin lesions, developmental and reproductive effects, and neoplasia. The expression of these responses is thought to be initiated by the binding of individual congeners (or ligands) with the Ah receptor. However, responsiveness of certain mouse strains to aromatic hydrocarbons is inherited in a simple autosomal-dominant mode and both enzyme induction and the toxic responses to 2,3,7,8-TCDD appear to segregate with the Ah locus (Poland and Glover 1980). For example, certain mouse strains, typified by C57XBL/6J, have an Ah receptor protein with a relatively high binding affinity for inducers of AHH such as 3-methylcholanthrene, β-naphthoflavone, 2,3,7,8-TCDD, and other isostereomers of 2,3,7,8-TCDD, and are sensitive to the toxic effects of these chemicals. In contrast, other mouse strains, such as DBA/2J, have an Ah receptor protein that has a lower ligand affinity (Okey et al. 1989), and are much less sensitive to the toxic effects of these compounds. The use of these mouse strains and strains differing only the Ah locus (congenic) has suggested that many of the responses elicited by these chemicals (e.g., enzyme induction, thymic involution, cleft palate formation, hepatic porphyria, and immunotoxicity) segregate with this Ah locus (Birnbaum et al. 1990; Kerkvliet et al. 1990b; Lin et al. 1991a, 1991b; Poland and Knutson, 1982; Swanson and

Bradfield 1993). More recent investigations using an Ah receptor-deficient mouse (Fernandez-Salguero et al. 1996) also support the role of this protein in mediating the toxicity of 2,3,7,8-TCDD and related halogenated aromatic hydrocarbons.

These genetic data strongly support the role of the Ah receptor in mediating the toxicity of 2,3,7,8-TCDD and related halogenated aromatic hydrocarbons. However, it has become clear that a comparison of the properties of the Ah receptor across species and tissues indicates that it is difficult to account for the species-specific sensitivity and diversity of the biological effects of 2,3,7,8-TCDD by characteristics of the receptor alone. There are several different forms of this protein in mice encoded by several different alleles of the same locus (Poland and Glover 1990; Poland et al. 1994). By analogy with the existence of multiple receptor forms in mice, it is reasonable to anticipate that the human population will also have different receptor forms. The extent to which these forms in mice and humans affect the types of responses elicited and the sensitivity to TCDD is not known. As indicated above, the Ah receptor has been identified in several human tissues and cell lines (Cook and Greenlee 1989; Harper et al. 1991; Harris et al. 1989a; Lorenzen and Okey 1991; Roberts et al. 1990). Although the general properties and function of the human Ah receptor (Harper et al. 1991) appear to be very similar to the rodent and other species (Denison et al. 1986a; Gasiewicz and Rucci 1984), some differences exist. For example, the molecular mass from a variety of human cell lines or tissues ranges from 106 to 110 kDa (Harper et al. 1991; Poland and Glover 1987; Wang et al. 1991), compared to approximately 95 kDa for C57XBL/6J mice or from Hepa-1 cells (Landers et al. 1989; Poland and Glover 1987, 1990; Prokipcak and Okey 1990), and 124 kDa from the hamster (Poland and Glover 1987). The same parameter for the nonresponsive DBA/2J mouse is approximately 104 kDa (Poland and Glover 1990). There is no known correspondence between molecular mass of the protein and its affinity for any ligand and/or ability to mediate a biological or toxicological response. Apparent affinity constants (measured under *in vitro* conditions) for 2,3,7,8-TCDD-human Ah receptor binding from various cell lines range from 3 to 15 nM compared with about 1 nM in cytosol from C57XBL/6J mice, 16 nM for the DBA/2J mouse, 0.1 nM for the guinea pig and 0.3 nM for the hamster (Cook and Greenlee 1989; Gasiewicz and Rucci 1984; Harper et al. 1991; Okey et al. 1989).

While the use of structure-activity relationships and mouse genetics are consistent with the notion that the binding of 2,3,7,8-TCDD and structurally-related chemicals to the Ah receptor is the initial event that leads to the induced synthesis of certain enzymes, it has only been through the work at the cellular and molecular biological levels that this has been substantiated. Furthermore, these investigations indicate that complex series of events regulate the activity of the receptor and it is likely that the differential regulation of these

may, at least in part, be responsible for the tissue- and species-specific nature of the response observed in mammals following the exposure to 2,3,7,8-TCDD and related compounds. Immunohistochemical studies have shown that in intact mouse hepatoma cells, the unliganded receptor resides in the cytoplasm, and that exposure to 2,3,7,8-TCDD leads to an accumulation of the receptor within the nucleus (Pollenz et al. 1994). However, the precise location of the unoccupied (i.e., without 2,3,7,8-TCDD bound) receptor in intact cells is still unresolved. The unoccupied AhR exists as a heteromeric complex with 2 molecules of another protein called 90 kDa heat-shock protein (hsp90) and another 43-kDa protein (Chen and Perdew 1994). Hsp90 appears to be necessary for maintaining the proper folding of the Ah receptor so it can bind ligand and limit the presence of another receptor form that is able to bind to DNA (Pongratz et al. 1992). The exact role of the 43-kDa protein is not yet known.

Binding of the Ah receptor by 2,3,7,8-TCDD initiates a series of as yet undefined events resulting in the dissociation of hsp90 and nuclear localization (Henry and Gasiewicz 1993; Pollenz et al. 1994; Pongratz et al. 1992). Results from experiments in genetically variant cells that respond poorly to 2,3,7,8-TCDD revealed a defect in 2,3,7,8-TCDD binding that results in an altered receptor. Other variants exhibited normal binding, but the liganded receptors do not bind DNA and do not accumulate in the nucleus (Hankinson 1979; Miller and Whitlock 1981). The finding that these variants have a defect in a protein, termed Arnt (Ah receptor nuclear transport protein) (Reyes et al. 1992), suggested that 2,3,7,8-TCDD responsiveness requires both a ligand-binding protein (the Ah receptor) and a second protein which mediates the binding of the liganded receptor to DNA (Whitlock 1993). Furthermore, the ligand-bound Ah receptor does not itself bind DNA (Gasiewicz et al. 1991). The Arnt protein does not bind 2,3,7,8-TCDD, nor does it bind to DNA in the absence of the liganded Ah receptor protein (Whitelaw et al. 1993). The role of the Arnt protein as a translocator of the receptor from cytoplasm to the nucleus has been questioned; instead, it has been shown that Arnt interacts with the liganded Ah receptor to form a heterodimeric DNA-binding protein complex that can bind DNA and activate gene transcription (Whitlock 1993). Other investigations have shown that phosphorylation/dephosphorylation of the Ah receptor and the Arnt protein may influence both heterodimerization and the binding of this complex to DNA (Berghard et al. 1993; Mahon and Gasiewicz 1995; Okino et al. 1992; Pongratz et al. 1991).

Most of the information regarding the sequence of events that follow 2,3,7,8-TCDD binding to the Ah receptor is based on analyses of induction of AHH activity, which results from enhanced transcription of the corresponding cytochrome P-450 1A1 (CYP1A1) gene. Stimulation of transcription occurs within minutes and does not require ongoing protein synthesis (Israel et al. 1985). These findings led to the

discovery of a dioxin-responsive regulatory DNA domain which has the properties of a transcriptional enhancer (Fisher et al. 1990; Jones et al. 1986; Neuhold et al. 1986). These specific DNA elements have been termed dioxin-responsive elements (DREs) and require both receptor protein and Arnt protein for enhancer function. DREs function in a chromosomal location distinct from that of the CYP1A1 gene (Fisher et al. 1989). In addition to the enhancer, the DNA upstream of the CYP1A1 gene has a second control element (a transcriptional promoter), which ensures that transcription is initiated at the correct site. Neither enhancer nor promoter functions in the absence of the other (Jones and Whitlock 1990). The fact that enhancer function requires both the receptor and Arnt protein, and that the liganded heteromeric form of the receptor shows increased affinity for the specific DNA sequence within the enhancer region suggested that the activation of the CYP1A1 gene involves the binding of the receptor heteromer to the DRE. This has been shown for the purified Ah receptor-Arnt protein complex (Henry et al. 1994). Analysis of the interaction of the Ah receptor with specific DNA domains indicates that the heteromer binds in a 1:1 ratio to the DRE (Denison et al. 1989). There is, however, no strict relationship between the affinity of the receptor heteromer for the DRE and the extent of enhancer activation (Neuhold et al. 1989; Shen and Whitlock 1992), which suggests that additional events, including DNA bending (Elferink and Whitlock 1990), must take place to activate transcription.

The use of many *in vitro* techniques for these studies has required removing the DNA regulatory elements from the chromosome environment, and this may produce misleading results. This led researchers to examine the protein-DNA interactions at the dioxin-responsive enhancer in intact cells. Results from these studies suggested that the inactive enhancer is relatively inaccessible to DNA-binding proteins in vivo and that exposure to 2,3,7,8-TCDD leads to a rapid binding of six receptor heteromers and other proteins to the enhancer upstream of the CYP1A1 gene (Wu and Whitlock 1993). It has also been shown that the CYP1A1 promoter, like the enhancer, is inaccessible in uninduced cells, and that exposure to 2,3,7,8-TCDD increases its accessibility to constitutively expressed proteins (Durrin and Whitlock 1989; Wu and Whitlock 1992). The 2,3,7,8-TCDD-induced change is not dependent on protein synthesis and is receptor- and Arnt-dependent. It has been suggested that the inaccessibility of the enhancer/promoter region in uninduced cells is due to its organization into nucleosomes (Ko et al. 1996; Morgan and Whitlock 1992). The mechanism by which the binding of liganded receptor heteromers to the enhancer alters chromatin structure leading to activation of transcription is unknown. Whitlock (1993) suggested that the DRE-bound receptor complex affects histones, thereby weakening the histone-DNA interactions and destabilizing nucleosomal structures. They also proposed that the receptor-enhancer interaction may alter the DNA structure of the enhancer/promoter region stabilizing it in a non-nucleosomal configuration.

The information resulting from the cloning and sequencing of the Ah receptor and Arnt has also expanded our knowledge of the molecular mechanisms whereby these proteins influence transcriptional activity (Hankinson 1995; Whitlock 1993). Both proteins are members of a class of transcription factors containing a basic helix-loop-helix (bHLH) structural motif as well as a PAS (Per-Arnt-Sim) domain. Both of these regions are involved in dimerization. The bHLH motif is also required for DNA sequence recognition, while the PAS domain contains the ligand-binding site (in the Ah receptor) and interacts with hsp90 (Coumaileau et al. 1995; Dolwick et al. 1993; Fukunaga et al. 1995; Whitelaw et al. 1993). Both the Ah receptor and Arnt have C-terminal regions that function in transcriptional activation, although their relative contributions may depend on the gene involved (Ko et al. 1996). Other members of the HLH-PAS family include hypoxia-inducible factor 1 alpha (HIF-a) and *Drosophila* protein Sim (Huang et al. 1993; Wang et al. 1995). All of the bHLH proteins identified to date are involved in transcriptional regulation, and have a variety of roles in tissue growth and differentiation processes. It is not yet clear whether the ligand-activated Ah receptor modulates gene expression only through its interaction with Arnt; it may have other dimerization partners. It is known that multiple heterodimerizations occur among several transcription factors, and that this multiplicity provides for the recognition of other DNA sequences and diversity of regulation of responsive genes. Arnt has been shown to dimerize with HIF-1a and Sim, and there appear to be several different isoforms of Arnt, two of which have been shown to interact with the Ah receptor (Henry et al. 1994; Hirose et al. 1996; Ireland et al. 1995; Swanson et al. 1995; Wang and Semanza 1995). However, as of yet, Arnt is the only protein that has been demonstrated to be a functional partner to the Ah receptor. Furthermore, the Ah receptor and Arnt appear to be co-expressed in a variety of tissues that have been examined (Abbott and Probst 1995; Abbot et al. 1995; Carver et al. 1994), suggesting co-dependence.

As indicated above, much of our understanding of the interaction of 2,3,7,8-TCDD with the Ah receptor and how it modulates gene expression has come mainly from the analysis of the regulation of the CYP1A1 gene. However, other studies have observed the presence of functional DREs in the genes that encode for CYP1A2 (Quattrochi et al. 1994), glutathione S-transferase Ya (Paulson et al. 1990), aldehyde-3-dehydrogenase (Takimoto et al. 1994), and NAD(P)H:quinone oxidoreductase (Favreau et al. 1991). In addition, an imperfect DRE is present in the regulatory region of the cathepsin D gene. In this case, the Ah receptor-Arnt complex may act as a repressor to prevent the binding of other transcription factors to nearby enhancer sequences (Safe 1995).

As discussed below, 2,3,7,8-TCDD-elicited activation of the Ah receptor has been shown to alter the transcription of a number of genes. However, only a few of these, as indicated above, are as yet known to contain functional DREs (Lai et al. 1996). While in some cases the regulatory regions of all of the genes known to be altered by 2,3,7,8-TCDD have not been thoroughly examined; in other cases, the regulatory regions are known not to contain the conserved consensus sequence for the DRE. It is possible that other dimerization partners exist and that different DNA sequences might be recognized. It is also possible that the 2,3,7,8-elicited modulation of many of these genes and processes may be secondary subsequent to the induction/repression of a DRE-containing gene. However, there is some evidence to suggest that other Ah receptor-dependent pathways may exist for the alteration of gene expression that may not be dependent upon the interaction of the Ah receptor with nuclear elements. It has been suggested that the interaction of 2,3,7,8-TCDD with the Ah receptor may initiate a phosphorylation/dephosphorylation cascade that may subsequently activate other transcription factors (Matsumura 1994). Enan and Matsumura (1995) reported an increase in protein kinase activity within 1–10 minutes following the addition of 2,3,7,8-TCDD to nuclear-free preparations of guinea pig adipose tissue. These results are consistent with previous investigations showing increased tyrosine kinase activity within minutes of 2,3,7,8-TCDD exposure (Bombick et al. 1988; Clark et al. 1991a; DeVito et al. 1994). Hsp90 has been found associated with a protein of 50 kDa (Chen and Perdew 1994; Whitelaw et al. 1993), and both have been shown to regulate the activity of pp60v-src, a tyrosine kinase (Brugge et al. 1983; Mimnaugh et al. 1995). c-Src has recently been reported to be a component of the unoccupied Ah receptor complex (Enan and Matsumura 1996). Thus, 2,3,7,8-TCDD may modulate signal transduction processes and gene expression by at least two pathways: through the direct interaction of the Ah receptor and its heterodimer partners with gene regulatory elements, and from the initiation of a phosphorylation/dephosphorylation cascade and the subsequent modulated activity of other nuclear transcription factors. It has yet to be determined which pathways may be more important in acute versus chronic responses to these compounds and/or during particular developmental periods. Nevertheless, together these data indicate that well regulated and conserved pathways exist for the transduction of cellular signals through the binding of 2,3,7,8-TCDD-like chemicals to the Ah receptor. Since the modulation of these pathways results in toxicity in response to 2,3,7,8-TCDD and related compounds, it is presumed that these chemicals cause these responses by either interfering with the normal function of some unknown endogenous ligand, and/or stimulating the signal transduction process at an inappropriate time and/or for an inappropriately long period of time.

As indicated in the preceding sections, cell/tissue death and necrosis are not prominent features of effects resulting from 2,3,7,8-TCDD exposure *in vivo* or *in vitro*. Hyperplasia, hypoplasia, metaplasia, and

dysplasia are the most common histopathological changes observed in animals (McConnell and Moore 1979). Likewise, under conditions *in vitro*, 2,3,7,8-TCDD-like compounds are potent in altering cellular differentiation and growth patterns for a number of different cell types including embryonic palatal epithelial cells (Abbott et al. 1989), keratinocytes (Gaido and Maness 1994), osteoblasts (Gierthy et al. 1994) and preimplantation embryos (Blankenship et al. 1993).

Despite the numerous tissue- and species-specific responses that have been observed and the elegant work on the molecular mechanisms mediating some of these, there exists a considerable gap between knowledge of these changes and the degree to which they are related to the biological and toxicological end points elicited by 2,3,7,8-TCDD and related compounds. These chemicals have been shown to alter the transcription and/or translation of a number of genes, including several oncogenes and those encoding growth factors, receptors, hormones, and drug-metabolizing enzymes (Birnbaum 1994a, 1994b). More recent investigations have noted effects on certain enzymes and proteins (e.g., kinases) involved in various signal transduction processes as well as cell cycle control (Birnbaum 1994a, 1994b; Weib et al. 1996). The elicited induction of certain drug metabolizing enzymes such as CYP1A1, CYP1A2, and CYP1B1 are some of the most sensitive responses observed in a variety of different animal species, including humans. Significantly increased levels of CYP1A1 mRNA have been observed as dosages as low as 0.1 ng/kg body weight (Kohn et al. 1993). However, the precise 2,3,7,8-TCDD-induced biochemical alterations that are causally responsible for the abnormal growth processes observed are not known. This is due predominantly to our incomplete understanding of the complex and coordinate molecular, biochemical, and cellular interactions that regulate tissue processes during development and under normal homeostatic conditions. Nevertheless, there is some evidence that many of these biochemical alterations may be relevant to altered growth responses observed. For example, changes in the EGF receptor have been seen in tissues from 2,3,7,8-TCDD-exposed animals and humans (Abbott and Birnbaum 1990a; Sewall et al. 1993; Sunahara et al. 1987). EGF and its receptor possess diverse functions relevant to cell transformation and tumorigenesis, and changes in these functions may be related to a number of dioxin-induced responses including neoplastic lesions, chloracne, and a variety of developmental effects. Likewise, the known ability of 2,3,7,8-TCDD directly or indirectly to alter the levels and/or activity of other growth factors and hormones, such as estrogen and thyroid hormone and their respective receptors, as well as enzymes involved in the control of cell cycle, may affect growth patterns in cells/tissues leading to adverse consequences. Thus, both the biochemical and biological data are consistent with the notion that 2,3,7,8-TCDD and related compounds are growth regulators.

2,3,7,8-TCDD and structurally related compounds elicit a wide range of adverse effects. Of the many adverse responses observed both in humans and experimental animals after exposure to 2,3,7,8-TCDD, the ones that appear at the lowest dose (more sensitive) are perhaps developmental/reproductive effects, alterations in the immune response, and neoplasia. An overview of the mechanism(s) involved in these effects is presented below. Detailed mechanistic explanations are beyond the scope of this profile. Some of the information has been extracted from recent reviews on these subjects (Kerkvliet 1995; Lucier et al. 1993a; Peterson et al. 1993).

Some common developmental effects attributed to 2,3,7,8-TCDD exposure in most laboratory mammals are thymic hypoplasia, subcutaneous edema, decreased prenatal growth, and prenatal mortality (Couture et al. 1990). In addition, there are other species-specific effects, such as cleft palate in mice. Any of these effects may result from actions on the mother, embryo/fetus, placenta, or any combination of these sites (Peterson et al. 1993). In general, developmental effects can be induced at exposure levels that are not maternally toxic; however, prenatal mortality appears to be associated with maternal toxicity. Structure-activity results for 2,3,7,8-TCDD and related halogenated hydrocarbons for overt fetotoxicity are consistent with an Ah receptor-mediated mechanism. Hydronephrosis is the most sensitive developmental response induced by 2,3,7,8-TCDD in mice and it can be observed at maternal doses that do not cause cleft palate or overt maternal toxicity (Abbott and Birnbaum 1989a; Abbott et al. 1987a, 1987b; Couture-Haws et al. 1991b; Neubert and Dillman 1972; Weber et al. 1985). Hydronephrosis *in vivo* is induced by a direct hyperplastic action of 2,3,7,8-TCDD on the uretic epithelium. This results in occlusion of the ureter and subsequent accumulation of urine in the kidney (Abbott et al. 1987a). As for cleft palate formation, 2,3,7,8-TCDD and related compounds seem to allow the palatal shelves to grow and make contact, but prevent the subsequent epithelial-to-mesenchyme transformation (Peterson et al. 1993; Pratt et al. 1984). Susceptibility to both hydronephrosis and cleft palate formation segregate with the Ah locus, and structure-activity relationships for dioxin-like compounds are consistent with those for Ah receptor binding (Safe 1990; Weber et al. 1985). Further details on the mechanism of 2,3,7,8-TCDD-induced hydronephrosis and cleft palate formation and the involvement of various growth factors in these responses can be found in Section 2.5.

Another sensitive system for 2,3,7,8-TCDD toxicity is the male reproductive system, and many of the effects observed were originally thought to be related to the ability of 2,3,7,8-TCDD to decrease plasma androgen concentrations (Mably et al. 1992a, 1992b, 1992c; Moore et al. 1985). The fact that 2,3,7,8-TCDD is transferred from mother to fetus and to neonates during lactation has a great impact on

the male reproductive system during early development. Testosterone and its metabolite dihydrotestosterone (DHT) are essential prenatally and/or early postnatally for imprinting and development of accessory sex organs and for initiation of spermatogenesis. Mably et al. (1992b) suggested that the demasculinization and feminization of sexual behavior and feminization by LH secretion is due to the fact that perinatal exposure to 2,3,7,8-TCDD impairs sexual differentiation of the central nervous system, which is dependent on the presence of androgens during early development. However, results from more recent studies suggest that the 2,3,7,8-TCDD-induced effects on the male reproductive system may be related to alterations in other systems such as brain amine content or in the expression of growth factors and receptors involved in urogenital cell system differentiation and proliferation (Bjerke et al. 1994a; Gray et al. 1995). Results from recent studies have also delineated the role of the Ah receptor in the development of 2,3,7,8-TCDD-induced alterations in the male reproductive tract (Roman and Peterson 1998; Roman et al. 1998a,b). A more detailed discussion of the mechanisms involved in these responses is presented in Section 2.5.

2,3,7,8-TCDD has been shown to block some estrogenic effects both *in vivo* and *in vitro*, and the relative potencies of 2,3,7,8-TCDD and related congeners are consistent with their relative binding affinities with the Ah receptor (Safe et al. 1991). Estrogens are necessary for normal uterine development and for maintenance of the adult uterus. The mechanism of these antiestrogenic effects seems to be related to a decrease in gonadal tissue responsiveness to estrogen (DeVito et al. 1992) rather than to increased metabolism of estrogen. Studies in cultured MCF-7 cells (estrogen-responsive cells derived from a human breast adenocarcinoma) revealed that the antiestrogenic activity of 2,3,7,8-TCDD could result from the increased metabolism of estrogens due to Ah receptor-mediated enzyme induction and/or a decreased number of estrogen receptors in the nucleus (Gierthy et al. 1987; Harris et al. 1989a, 1990; Safe et al. 1991; Zacharewski et al. 1991, 1992). More recent data indicates that in some cases 2,3,7,8-TCDD may block the effects of estrogen through the ability of the 2,3,7,8-TCDD-bound Ah receptor-Arnt complex to interfere with the estrogen receptors binding to enhancer elements within the regulatory regions of estrogen-responsive genes (Krishnan et al. 1995; Safe 1995). Thus, the mechanism by which 2,3,7,8-TCDD and related compounds may block certain effects of estrogen may be varied depending on the particular gene, response, and tissue. Under some conditions, 2,3,7,8-TCDD may also cause estrogen-like responses. For example, the treatment of mice with an appropriate dosage of 2,3,7,8-TCDD or estrogen results in thymic involution and modulation of particular bone marrow stem cell markers (Silverstone et al. 1994). However, the mechanism by which these compounds act are clearly different since potent antiestrogens block the effects of estrogen treatment without affecting 2,3,7,8-TCDD-elicited

responses (Frazier et al. 1994). Similarly, the effects of 2,3,7,8-TCDD on the development of external genitalia in rats are similar to the effects observed in animals exposed to potent estrogen-like chemicals (Gray and Ostby 1995).

Extensive evidence suggests that the immune system is a sensitive target for toxicity of 2,3,7,8-TCDD and structurally related halogenated aromatic hydrocarbons (Kerkvliet 1995). Exposure to 2,3,7,8-TCDD can increase susceptibility to bacterial (Thigpen et al. 1975; Thomas and Hinsdill 1979; White et al. 1986), viral (Clark et al. 1983; House et al. 1990), parasitic (Tucker et al. 1986), and neoplastic disease (Luster et al. 1980). However, the specific immunological functions affected by 2,3,7,8-TCDD in most of the host-resistance models have not been fully defined. Thymic involution is characteristic of exposure to 2,3,7,8-TCDD and structurally related chemicals in all species examined. There is experimental evidence showing that immune suppression in rodents occurs at lower doses of 2,3,7,8-TCDD when the animals are exposed perinatally as compared with rodents exposed as adults, and that the prenatal effects are selective for T-cell-mediated immunity (Clark et al. 1983; Faith and Moore 1977; Vos and Moore 1974). The mechanism for 2,3,7,8-TCDD-induced thymic atrophy is not completely understood. There is evidence in rats suggesting that the 2,3,7,8-TCDD-induced effect is not mediated by an effect on the pituitary or adrenal glands, or from decreased production of thymic hormones (Van Logten et al. 1980; Vos et al. 1978). There appear to be multiple mechanisms involving alterations in thymocyte differentiation (Blaylock et al. 1992; Cook et al. 1987a; Denker et al. 1985; Greenlee et al. 1985), thymocyte proliferation (Lundberg et al. 1990), and migration of lymphocyte stem cells (Fine et al. 1990).

A commonly used assay for immunotoxicity is the suppression of the antibody response to SRBC. The magnitude of the anti-SRBC response depends on the interactions of antigen-presenting cells (i.e., macrophages), regulatory T-lymphocytes (i.e., helper and suppressor T cells), and B-lymphocytes (i.e., antibody-producing cells). Results from experiments *in vivo* suggested that the target for 2,3,7,8-TCDD in the antibody response to either SRBC or tumor cells is the T-cell and/or macrophage components rather than the B-cell (Kerkvliet and Brauner 1987; Kerkvliet et al. 1996). Although the effects of 2,3,7,8-TCDD on B-cell function *in vivo* have not been examined, *in vitro* studies suggest that 2,3,7,8-TCDD inhibits the terminal differentiation of B cells via alteration of an early activation event, perhaps increased protein phosphorylation and tyrosine kinase activity (Clark et al. 1991a; Kramer et al. 1987; Luster et al. 1988; Morris et al. 1991). Macrophage functions, examined *ex vivo*, generally have been found to be resistant to suppression by 2,3,7,8-TCDD (Mantovani et al. 1980; Vos et al. 1978). There is also evidence suggesting

that inflammatory cells may be activated by 2,3,7,8-TCDD via enhanced production of inflammatory mediators such as interleukin 1 and tumor necrosis factor (Clark et al. 1991b; Taylor et al. 1992).

Extensive research has been conducted on the role of the Ah locus in immunotoxicity of 2,3,7,8-TCDD and related compounds, and overall, the data linking 2,3,7,8-TCDD-induced immunotoxicity to the Ah receptor are convincing. For example, Vecchi et al. (1983a) reported that the antibody response to SRBC was greatly suppressed by 2,3,7,8-TCDD in C57BL/6J mice, but not as much in DBA/2J mice. Results from structure-activity studies for the SRBC response with CDDs that contaminate technical grade pentachlorophenol supported an Ah receptor-mediated effect (Kerkvliet et al. 1985). The Ah receptor was also found to be involved in the suppression of the antibody response to lipopolysaccharide (Kerkvliet et al. 1990a); and the cytotoxic T-lymphocyte response, and suppression of the latter by dioxin-like PCBs, correlated with relative-binding affinities for the Ah receptor (Kerkvliet et al. 1990b). An additional response found to segregate with Ah-responsiveness was the cytotoxic response to activated neutrophils (Ackermann et al. 1989). It is important to mention that results from some studies suggest that suppression of the *in vitro* antibody response may not be Ah receptor-mediated. For example, Holsapple et al. (1986a) reported that the magnitude of the response was comparable using cells from responsive mice relative to nonresponsive mice. Also, 2,7-dichlorodibenzo-p-dioxin, a congener with little affinity for the Ah receptor, was equipotent with 2,3,7,8-TCDD in suppressing the *in vitro* response. A similar conclusion was reached by Davis and Safe (1991), who found that a series of halogenated aromatic hydrocarbons, which had a >14,900-fold difference in *in vivo* immunotoxic potency, were equipotent *in vitro* in suppressing the anti-SRBC response using cells from either responsive or nonresponsive mice. Although these results suggest a possible role of non-Ah receptor mechanisms, the studies fail to rule out a role of the Ah receptor. The variable effects of 2,3,7,8-TCDD *in vitro* may have been due to factors such as media components or procedures used to prepare cell suspensions. Kerkvliet (1994) suggested that "the difficulty in demonstrating consistent, direct effects of 2,3,7,8-TCDD *in vitro* on lymphocytes, the dependence of those effects on serum components, and the requirements for high concentrations of 2,3,7,8-TCDD are all consistent with an indirect mechanism of 2,3,7,8-TCDD on the immune system." One potentially important indirect mechanism operates through effects on the endocrine system. Glucocorticoids, sex steroids, T4, growth hormone, and prolactin have been shown to regulate immune responses, and 2,3,7,8-TCDD has been shown to alter the activity of all of them (see also sections on endocrine and reproductive effects).

There is sufficient evidence that 2,3,7,8-TCDD is carcinogenic in animals, and the overall epidemiological database suggests that the incidence of certain types of cancer may be increased in humans by exposure to

2,3,7,8-TCDD (Hardell et al. 1994; Lucier et al. 1993a). The mechanism of 2,3,7,8-TCDD carcinogenicity has not been fully elucidated, but there is considerable evidence indicating that it does not involve direct damage to DNA through formation of DNA adducts. The criteria for designating 2,3,7,8-TCDD as a nongenotoxic carcinogen are based on the following: studies using extraordinarily sensitive analytical methods have been unable to detect DNA adducts in rodent tissue after exposure to 2,3,7,8-TCDD (Randerath et al. 1988; Turteltaub et al. 1990), numerous studies have demonstrated that 2,3,7,8-TCDD is not mutagenic in the *Salmonella*/Ames test with or without an activating system (Giri 1986; Wassom et al. 1978), and 2,3,7,8-TCDD is a potent tumor promoter and a weak initiator or noninitiator in the two-stage models for liver (Flodstrom and Ahlborg 1989; Lucier et al. 1991; Pitot et al. 1980) and skin (Poland et al. 1982). Instead, it has been proposed that 2,3,7,8-TCDD might alter the capacity of both exogenous and endogenous substances to damage the DNA by inducing CYP1A1- and CYP1A2-dependent drug-metabolizing enzymes. In some cases, enzyme induction will lead to increased formation of DNA-damaging metabolites, as appears to be the case in the two-stage model in rat liver and mouse skin (Flodstrom and Ahlborg 1992; Hebert et al. 1990; Poland and Knutson 1982; Poland et al. 1982). A recent study suggested that the induction of CYP1A1 may also lead to an increase in oxygen radicals and consequent oxidative DNA damage that could lead to mutation and cancer (Park et al. 1996). However, in many cases in which induction leads to increased rate of detoxification, the opposite will occur, as demonstrated by Cohen et al. (1979) for benzo[a]pyrene. The protection afforded by preinduction of CYP1A1 by 2,3,7,8-TCDD appears to be Ah receptor-mediated since it does not occur in mice deficient with low-affinity Ah receptor (Kouri et al. 1978). It should be noted that results from structure-activity studies for 2,3,7,8-TCDD and related compounds strongly suggest that the hepatocarcinogenic actions of 2,3,7,8-TCDD are Ah receptor-dependent (Flodstrom and Ahlborg 1992; Hebert et al. 1990; Poland et al. 1982; Poland and Knutson 1982). The role of CYP1A2 induction is less clear than for CYP1A1. Some have suggested that the liver carcinogenicity of 2,3,7,8-TCDD in intact female rats, but not male rats or ovariectomized female rats, could be explained in part by the formation of toxic catechol estrogens from 17β-estradiol, a reaction catalyzed by CYP1A2 (Lucier et al. 1993a). This is also consistent with the finding that CYP1A2 is induced in liver but not in extrahepatic organs.

The role of the EGF receptor in 2,3,7,8-TCDD-induced carcinogenicity has also been examined. EGF is a mitogen that stimulates the generation of mitotic signals in both normal and neoplastic cells, and its receptor and ligands have a variety of functions involved in cell transformation and tumorigenesis. It has been shown that 2,3,7,8-TCDD decreases the binding capacity of the plasma membrane EGF receptor for its ligand without changing the affinity constant (Abbott and Birnbaum 1990a; Hudson et al. 1985; Lin et

al. 1991a; Madhukar et al. 1984). The mechanism involved is not completely understood, but it appears that 2,3,7,8-TCDD does not decrease EGF receptor mRNA (Lin et al. 1991a). The effects of 2,3,7,8-TCDD on the EGF receptor have been shown to require the Ah receptor (Lin et al. 1991a). The EGF receptor-like response produced by 2,3,7,8-TCDD is consistent with the idea that 2,3,7,8-TCDD increases the generation of cellular mitotic signals which may, in part, be responsible for the tumor-promoting actions of 2,3,7,8-TCDD.

The possible role of UDP-glucuronyltransferases (UDPGT) on the carcinogenicity of 2,3,7,8-TCDD has also been studied. UDPGTs are thought to be a deactivation pathway for many environmental chemicals and endogenous substances such as steroid hormones by increasing their water solubility, thereby facilitating excretion by a conjugation reaction. 2,3,7,8-TCDD induces synthesis of at least one UDPGT isozyme (Lucier et al. 1986) by a Ah receptor-mediated mechanism (Bock 1991). For example, the oncogenic effect of prolonged stimulation of the thyroid by TSH has been attributed to decreased levels of T4 due to UDPGT induction. Decreased T4 levels induce the pituitary gland to respond by secreting increased amounts of TSH. This is consistent with results from rodent studies in which 2,3,7,8-TCDD and other inducers of UDPGT decreased T4 levels in blood, which is associated with increased TSH levels (Henry and Gasiewicz 1987). Lucier et al. (1986) showed that in rats, the shape of the dose-response curve for induction of UDPGT by 2,3,7,8-TCDD is similar to that of CYP1A1 induction. Kohn et al. (1996) constructed a physiologically based model to investigate the hypothesis that induction of UDPGT by 2,3,7,8-TCDD may ultimately lead to a tumorigenic response in the thyroid of rats. The model included compartments for the thyroid and thyroxine-sensitive tissues, secretion and tissue uptake of thyroid hormones, binding of T3 and T4 to proteins in blood and tissues, iodination of iodothyronines, and glucuronidation of T4 by hepatic UDPGT. The model accurately predicted the effects of 2,3,7,8-TCDD on blood thyroid hormone concentrations, hepatic UDPGT activity, and the consequent increase of serum TSH. This was consistent with the observation that induction of UDPGT results in increased glucuronidation and biliary excretion of T4. The results of Kohn et al. (1996) provided further support to the hypothesis that induction of UDPGT is an early event in the generation of thyroid tumors by 2,3,7,8-TCDD in the rat.

There is evidence that some carcinogenic responses to 2,3,7,8-TCDD are related to effects of 2,3,7,8-TCDD on the estrogen receptor (ER) and on estrogen metabolism. The responses appear to be tissue-specific as illustrated by the fact that in rats 2,3,7,8-TCDD increases liver tumor incidence, but decreases tumor incidence in mammary glands, the uterus, and pituitary gland (Kociba et al. 1978a). In

rats, a single dose of 2,3,7,8-TCDD decreases the binding capacity of the hepatic ER for estrogens (Romkes and Safe 1988; Zacharewski et al. 1991, 1992). This response seems to be Ah receptor-mediated since 2,3,7,8-TCDD was much more effective in decreasing hepatic ER binding in C57BL/6J mice (responsive strain) than in congenic mice with low-affinity Ah receptor (Lin et al. 1991b). 2,3,7,8-TCDD also decreased rat hepatic ER in a 30-week-duration study (Clark et al. 1991b). The single ED_{50} for decreasing hepatic ER binding is similar to that for CYP1A1 induction, loss of plasma membrane EGF receptor, and induction of UDPGT (Lucier et al. 1993a). The relationship, however, between changes in concentration and cell proliferation have yet to be fully evaluated. In reproductive tract tissues, 2,3,7,8-TCDD decreases tumor incidences by a mechanism possibly involving increased estrogen metabolism as a consequence of UDPGT induction. Increased estrogen degradation was also observed in the MCF-7 breast cancer cell line after addition of 2,3,7,8-TCDD (Gierthy et al. 1988).

As indicated above, a substantial body of evidence is consistent with the premise that the Ah receptor mediates the biological effects of 2,3,7,8-TCDD. Furthermore, this evidence indicates that a response to this chemical requires the formation of a ligand-receptor complex. 2,3,7,8-TCDD-receptor binding appears to obey the law of mass action and, therefore, depends on the concentrations of both ligand and receptor in the target cell, and the binding affinity of the ligand for the receptor. In principle, and according to the law of mass action, some active 2,3,7,8-TCDD-Ah receptor complexes may form even at very low levels of exposure. In reality, however, it is likely that at some finite concentration of 2,3,7,8-TCDD, the formation of 2,3,7,8-TCDD-receptor complexes will be insufficient to elicit detectable or biologically relevant effects due to dependence on other factors (e.g., Arnt binding and DRE binding) and events (e.g., mRNA transcription and protein synthesis) necessary for the cascade of a signal transduction process to occur. Recent studies have indicated no evidence of a threshold for some relatively simple biochemical responses to 2,3,7,8-TCDD such as CYP1A1 induction (Kohn et al. 1993). However, this cannot yet be interpreted as an absence of a threshold since it is possible that either insufficiently low concentrations of 2,3,7,8-TCDD were used, or the background level of 2,3,7,8-TCDD equivalents (including any putative endogenous ligand) is already above the threshold level (even in experimental animals). Events leading to a toxic response that are subsequent to 2,3,7,8-TCDD-receptor binding and the induction of a particular biochemical event such as CYP1A1 activity, may or may not exhibit a linear response to 2,3,7,8-TCDD since these events are likely additionally dependent on multiple and complex biochemical, cellular, and tissue changes that may or may not be dependent on saturable processes. Further information will be required to determine if other responses to 2,3,7,8-TCDD, both biochemical and biological, do or do not demonstrate threshold behavior.

It is generally accepted that the toxicity of CDDs, including 2,3,7,8-TCDD, is due mainly to the parent compound. Hydroxylated metabolites lack the activity of the parent compound, suggesting that metabolism is a detoxification process necessary for the biliary and urinary excretion of these compounds. For instance, dog metabolites of 2,3,7,8-TCDD administered to guinea pigs had at least 100 times less acute toxic potency than the parent compound (Weber et al. 1982). In another study, two hydroxylated metabolites of 2,3,7,8-TCDD showed no significant effect on Ah receptor-mediated responses, such as body weight loss, thymus atrophy, or liver or spleen weight in male Wistar rats at doses as high as 5,000 µg/kg (Mason and Safe 1986a). One of the metabolites, 2-hydroxy-3,7,8-TrCDD, induced CYP1A1-related enzyme activities only at very high dose levels (1,000 and 5,000 µg/kg), whereas the other metabolite, 2-hydroxy-1,3,7,8-TCDD, lacked inducing capacity. Structure-activity studies of 7-substituted 2,3-CDDs, including the hydroxylated congeners, showed that the binding affinities of the hydroxylated congeners for the Ah receptor were significantly lower than those of the corresponding chlorine analogs (Denomme et al. 1985). Similar results were obtained in an additional study using hepatic cytosol from rat, mouse, hamster, and guinea pig (Romkes et al. 1987).

There is some evidence that hydroxylated metabolites of CDDs interfere with the transport of T4 in blood by a mechanism unrelated to the Ah receptor (Lans et al. 1993, 1994). These investigators showed that hydroxy-CDDs with chlorine substitution adjacent to the hydroxy group (e.g., 7-hydroxy-2,3,8-TrCDD, 2-hydroxy-1,3,7,8-TCDD, and 3-hydroxy-2,6,7,8-TCDD) showed similar or higher relative binding potency than T4 for the thyroid hormone transport protein transthyretin (TTR) in an *in vitro* assay using purified human TTR (Lans et al. 1993). In a subsequent study, they found that none of several hydroxylated CDDs tested inhibited T4 binding to thyroxin-binding globulin, the major T4-transporting plasma protein in humans, as opposed to TTR in rodents (Lans et al. 1994). This clearly indicated that hydroxylated CDDs may cause different effects in rodents and humans.

The possibility exists that reactive epoxide intermediates of 2,3,7,8-TCDD that may be formed as a result of metabolism are involved in 2,3,7,8-TCDD-induced carcinogenicity by covalently binding to DNA. However, this appears unlikely since, as previously mentioned, studies using extraordinarily sensitive analytical methods have been unable to detect DNA adducts in rodent tissue after exposure to 2,3,7,8-TCDD (Randerath et al. 1988; Turteltaub et al. 1990), and the fact that 2,3,7,8-TCDD is not mutagenic in the *Salmonella*/Ames test with or without an activating system (Giri 1986; Wasson et al. 1977).

2.4.3 Animal-To-Human Extrapolations

As discussed in the introduction to Section 2.1, there are a number of limitations in the human database; for most health effects, the data are inadequate to assess the potential for humans having a particular effect. Because the human data are incomplete, hazard and risk must be extrapolated across species. A large number of adverse effects have been observed in animals, and most have been observed in every experimental animal species tested, if the appropriate dose is administered. This is illustrated in Table 2-8 for 8 major effects associated with CDD toxicity (acute lethality, hepatotoxicity, wasting syndrome, chloracne, immunotoxicity, reproductive toxicity, developmental toxicity, and cancer). With the exception of acute lethality in humans, positive responses have been observed in each tested species, when a response has been investigated. Despite the similarities in hazard response between different species, large species differences in sensitivity have been observed. Comparisons of species sensitivity demonstrate that no species is consistently sensitive or refractory for all effects and, for some effects, there is a small range of species sensitivity. As presented in Table 2-9, the range of LD_{50} values for 6 commonly tested animal species spans several orders of magnitude. Guinea pigs have the lowest LD_{50} value (0.6 µg/kg) and hamsters have the largest (1,157 µg/kg). However, if these outliers are removed, the range of LD_{50} values for mice, monkeys, rabbits, and rats is less than an order of magnitude (22–115 µg/kg). In contrast, the range of LOAELs for reproductive toxicity (abortions, resorptions, pre- and post-implantation losses) spans approximately an order of magnitude with rats (0.125 µg/kg) being the most sensitive and guinea pigs the least sensitive (1.5 µg/kg; NOAEL of 0.15 µg/kg). These data suggest that even though some effects have wide ranges of sensitivity, for most of the effects, the LOAELs for the majority of species cluster within an order of magnitude (Table 2-9).

It is generally accepted that the Ah receptor plays a role in mediating many toxic responses attributed to exposure to CDDs (for additional information on the mechanisms of toxicity, see Section 2.4.2). For some responses, receptor binding appears necessary but may not be sufficient to result in downstream biological effects. Ah receptors have been found in most species, including humans, monkeys, rats, mice, hamsters, rabbits, and guinea pigs (Denison et al. 1986a; Landers and Bunce 1991). A simple way to explain sensitivity differences among species to 2,3,7,8-TCDD and related compounds, at least for Ah receptor-mediated responses, would be to assume that they are related to differences in receptor levels in target tissues and/or to differences in the affinity of binding of the specific CDD congeners. However, experimental data indicate that differences in such parameters cannot explain marked differences to CDD toxicity across species. For example, single dose LD_{50}s range from 0.6 µg/kg in guinea pigs to 1,157 µg/kg in

Table 2-8. Comparison of Health Effects Among Species Exposed to CDDs

Effect	Human	Monkey	Rat	Mouse	Hamster	Dog	Rabbit	Guinea pig	Mink
Acute lethality	–	+	+	+	+	+	+	+	+
Hepatotoxicity	+	+	+	+	ND	ND	ND	+	+
Wasting syndrome	**	+	+	+	+	ND	ND	+	+
Chloracne	+	+	ND	+	ND	ND	+	ND	ND
Immunotoxicity (thymic atrophy)	ND	+	+	+	+	ND	ND	+	ND
Reproductive toxicity (loss of pregnancy)	**	+	+	+	ND	ND	+	+	ND
Developmental toxicity (fetal toxicity and/or mortality)	**	+	+	+	+	ND	+	+	ND
Cancer	+	ND	+	+	+	ND	ND	ND	ND

+ = observed; – = not observed; ** = some effects have been observed but data limitations preclude drawing conclusions; ND = no data

Table 2-9. Comparison of LOAELs Among Animal Species Following a Single Oral Dose of 2,3,7,8-TCDD

	LOAEL (µg/kg)			
Species	Death (LD_{50})	Immunological effects (thymic atrophy)	Reproductive effects (abortions, resorptions, or pre- and post-implantation losses)	Developmental effects
Guinea pig	0.6 (Schwetz et al. 1973)	0.8 (Hanberg et al. 1989)	1.5 (Olson and McGarrigle 1992)	1.5 fetal mortality (Olson and McGarrigle 1992)
Hamster	1157 (Olson et al. 1980a)	48 (Hanberg et al. 1989)	ND	1.5 hydronephrosis (Olson and McGarrigle 1992)
Mouse	100 (Weber et al. 1995)	280 (Hanberg et al. 1989)	1.0 (Smith et al. 1976)	1 hydronephrosis (Moore et al. 1973)
Monkey	70 (1/3 died) (McConnell et al. 1978a)	70 (McConnell et al. 1978a)	1.0 (McNulty 1984)	1 fetal death (McNulty 1984)
Rabbit	115 (Schwetz et al. 1973)	ND	0.25 (Giavini et al. 1982)	ND
Rat	22 (Schwetz et al. 1973)	26 (Hanberg et al. 1989)	0.125 (Sparschu et al. 1971a)	0.064 impaired development of male reproductive system (Mably et al. 1992b, 1992c)

ND = no data

hamsters, but the affinity with which 2,3,7,8-TCDD binds to the Ah receptor from guinea pigs is not significantly different from the affinity with which 2,3,7,8-TCDD binds to the hamster Ah receptor (Denison et al. 1986a). In addition, there are no significant differences in the level of the hepatic Ah receptor between the two species, suggesting that in addition to species differences in receptor levels and in their affinities for the ligand, differences in species sensitivity to 2,3,7,8-TCDD may be determined by some event or events occurring after the initial binding of 2,3,7,8-TCDD to the Ah receptor. These late events may involve a complicated interplay between genetic and environmental factors which may be key determinants of 2,3,7,8-TCDD biological potency and toxicity. Factors unrelated to the Ah receptor, such as toxicokinetic differences, may also account for some of the observed species differences (for additional information, see Section 2.4.2). The Ah receptor has been identified in many human tissues and human cell lines (Okey et al. 1994). However, considerable individual differences in the expression levels of both Ah receptor and Arnt mRNAs have been found in human tissues (Hayashi et al. 1994). Furthermore, based on findings in inbred mice, polymorphism in the Ah receptor probably exists in humans, so that a concentration of TCDD that produces a response in one individual may not do the same in another (Whitlock 1993). This could explain why there was a wide range of serum 2,3,7,8-TCDD levels among Seveso residents where the occurrence of chloracne was sporadic over a generally wide range of doses (Mocarelli et al. 1991).

The weight of evidence from animal species comparisons and mechanistic data indicates that caution should be exercised when extrapolating from animals to humans. Some theoretical models indicate a basis for extrapolating from animals to humans, but such models have not been validated; there is wide variation in the results of different models; and a great deal of uncertainty remains regarding whether valid, predictive extrapolations can be made. It is reasonable to assume that humans will not be the most sensitive responder or be refractory to all effects, and that they will have a wider range of response due to increased heterogeneity. Levels of exposure to CDDs that produce toxicity in experimental animals cannot be directly compared to levels associated with adverse health effects in humans because most epidemiologic studies do not provide adequate data to estimate CDD exposures in the studied populations. However, the CDD body-burden history can sometimes be estimated in epidemiology studies from reported serum or adipose concentrations and empirically based assumptions regarding whole-body elimination kinetics of CDDs (as discussed in the introduction to Section 2.1). Comparisons between estimated adverse body burdens of CDDs and related compounds (CDFs, PCBs) in experimental animals and humans have shown that humans and animals appear to respond to similar body burdens (DeVito et al. 1995). As presented in Table 2-10, the adverse effect levels identified in humans are typically within a factor of 10 of the body

Table 2-10. Comparison of Body Burden Effect Levels Among Humans and Animals

Category	Effect	Species	Duration of exposure	Body burden[a,b] (ng/kg)	Reference
Dermal	Chloracne	Human	<1 year	2,876	Mocarelli et al. 1991
	Chloracne	Human	NS	1,480 262	Schecter et al. 1993
	Chloracne	Human	11 years	646	Jansing and Korff 1994
	Chloracnegenic effects	Monkey	3 weeks	530[c]-N 1,650-L	McNulty 1984
	Chloracnegenic effects	Monkey	9 months	1,910[c]	Allen et al. 1977
Immunological	Immunosuppression	Human	6.5 years	207–244	Tonn et al. 1996
	Decreased cell-mediated immunity	Mouse	4 weeks	9,100[d]	Vos et al. 1973
	Decreased humoral immunity	Guinea pig	8 weeks	670	Vos et al. 1973
	Decreased effector and memory T cells	Mouse	14.5 months	60[d]	Oughton et al. 1995
Reproductive	Change in sex ratio of children	Human	<1 year	119 174	Mocarelli et al. 1996
	Increased prevalence of high luteinizing hormone and low testosterone levels	Human	≥15 years	31-6,600	Egeland et al. 1994
	Increased incidence of abortions	Monkey	3 weeks	330[c]-N 1650-L	McNulty 1984
	Increased incidence of abortions	Monkey	4 years	270[c]	Bowman et al. 1989b; Hong et al. 1989
	Decreased plasma testosterone levels	Rat	once	12,500[f]	Moore et al. 1985
Cancer	Increased cancer mortality risk	Human	≥1 year	310-1,858	Fingerhut et al. 1991
	Increased cancer mortality risk	Human	NS	≥1,000	Ott and Zober 1996
	Increased cancer mortality risk	Human	≥20 years	71-945	Manz et al. 1991
	Liver, lung, hard palate cancer	Rat	2 years	2,770[f]	Kociba et al. 1978a

[a] Calculations of human body burdens are described in the footnotes to Table 2-1

[b] Animal body burdens were estimated as follows: $Cb = (I \cdot a \cdot f)/k$, $f = 1-(e^{-kt})$; where, C_b is the TCDD body burden (ng/kg bw), I is TCDD intake (ng/kg-day), a is the gastrointestinal absorption fraction, f is the fraction of steady-state body burden, k is the whole body elimination rate constant for TCDD (day^{-1}, $ln2/t_{1/2}$), and t is the exposure duration (day)

[c] Assumed parameter values for monkeys: a = 0.8 (value for rats from Van den Berg et al. 1994), $t_{1/2}$= 391 days (Bowman et al. 1989b)

[d] Assumed parameter values for mice: a = 0.8 (Curtis et al. 1990), $t_{1/2}$= 11 days (Birnbaum 1986)

[e] Assumed parameter values for guinea pigs: a=0.5 (Van den Berg et al. 1994), $t_{1/2}$ = 94 days (Olson 1986)

[f] Assumed parameter values for rats: a=0.8 (Van den Berg et al. 1994, $t_{1/2}$ = 24 days (Van den Berg et al. 1994)

L = LOAEL; N = NOAEL;NS = not specified

burdens associated with similar effects in animals. The data in Table 2-10 should be interpreted cautiously and should not be taken to suggest that humans are more sensitive than experimental animals. The human body burdens were estimated from serum 2,3,7,8-TCDD levels measured many years after exposure termination using empirically based assumptions; small differences in one or more assumption can result in large differences in the estimated body burdens. For example, the body burden of 945 ng/kg in the Manz et al. (1991) study was estimated using a half-life of 8.5 years; if the half-life of 7.1 years were used, the estimated body burden would have been 1606 ng/kg. Additionally, individual serum 2,3,7,8-TCDD levels and length of time between exposure termination and measurement of serum 2,3,7,8-TCDD levels (latency) were not available for a few epidemiology studies, and mean serum levels and latency periods were used to estimate body burdens. The use of mean values rather than individual values and empirically based assumptions may have resulted in an over- or underestimation of actual body burdens. Conversely, in the animal studies, actual exposure levels were known and there is greater confidence in the estimated body burdens. An acute high-dose exposure would produce higher peak serum lipid 2,3,7,8-TCDD and target tissue levels than chronic exposure to lower levels, although the body burdens may be similar. Thus, it may be misleading to compare adverse-effect body burdens from acute studies to those identified in chronic studies. Another issue which needs to be considered in comparing the human and animal adverse-effect body burdens is that this is comparison of LOAELs not a comparison of threshold levels, and free-standing LOAELs may not accurately predict threshold levels.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview

The primary route of exposure to CDDs for the general population is the food supply. This type of exposure is the main contributor to the background exposure. Background exposure refers to exposure of the general population who are not exposed to readily identifiable point-sources of CDDs that result in widespread, low-level circulation of CDDs in the environment. It is generally accepted that the contribution of inhalation and direct contact with CDDs to the body burden of the general population is not more than a few percent. However, inhalation and direct contact represent major exposure routes in cases of occupational or accidental exposures. A background exposure level of approximately 0.7 pg 2,3,7,8-TCDD/kg/day (assuming a 70 kg reference body weight) has been estimated for the general population in the United States (Travis and Hattemer-Frey 1987). If other CDD and CDF congeners are included, the background exposure level increases to approximately 18–192.3 pg TEQ/day (0.26–2.75

pg/kg/day using a 70 kg reference body weight) (Schecter et al. 1994b) (for additional information on TEQ, see the Toxic Equivalency Factor [TEF] and Toxic Equivalents [TEQ] subsections). The inclusion of dioxin-like PCBs further raises the estimate to 3–6 pg TEQ/kg/day (Beck et al. 1989a; WHO 1991). The average concentration of 2,3,7,8-TCDD in the adipose tissue of the U.S. population is 5.8 pg/g lipid (Orban et al. 1994). For all TEQ congeners, excluding dioxin-like PCBs, the national average was approximately 28 pg TEQ/g lipid. In humans, the partitioning ratio of 2,3,7,8-TCDD between adipose tissue lipid and serum lipid is approximately 1 and remains near unity over at least a 1,000-fold concentration range over background levels (Patterson et al. 1988). This makes serum lipid an accurate and more practical measure of body burden than adipose tissue lipid.

Data on human health effects of CDDs are derived from a variety of sources, including case reports and epidemiologic studies using case-control, cross-sectional, and cohort designs. While case-control and cohort studies have been used to investigate increases in the incidence of cancers among populations exposed to 2,3,7,8-TCDD, nonmalignant effects have been examined in cross-sectional medical studies. In many of the earliest studies, the magnitude of exposure-response relationships could not be adequately assessed for a number of reasons, including small sample size, poor participation, selection of inappropriate controls, the inability to identify confounding exposures, and short latency periods (especially important for assessment of cancer). A long interval between exposure and examination (up to 40 years in some cases) is a serious limitation when assessing noncancer responses since responses that resolve with time might not be detected at the time of the examination. On the other hand, health conditions that may be present at the time of examination may be totally unrelated to past exposure to 2,3,7,8-TCDD. An additional limitation was the inability to quantify exposure. However, serum or adipose tissue levels of 2,3,7,8-TCDD have been measured in more recent cross-sectional studies of U.S. chemical workers (Sweeney et al. 1989), Ranch Hand veterans (USAF 1991), and Missouri residents (Webb et al. 1989). Using a standard half-life equation and assuming a one-compartment model and first-order kinetics, the half-life for 2,3,7,8-TCDD in humans has been estimated to be 8.7 years (Michalek et al. 1996). By knowing the half-life, estimates of body burdens at the time of exposure can be back-calculated. These estimates, however, should be used with caution since little information exists regarding the metabolism of 2,3,7,8-TCDD in humans. In addition, there are considerable differences in the elimination half-lives for these chemicals among individual humans.

For 2,3,7,8-TCDD, the majority of the effects have been reported among occupationally exposed individuals such as producers or users of chemicals in which 2,3,7,8-TCDD might have occurred as

impurities, and among residents of communities contaminated with 2,3,7,8-TCDD. Effects that have been associated with exposure to materials contaminated with 2,3,7,8-TCDD in some studies include cancer; dermal, hepatic and thyroid effects; effects on serum lipids; diabetes; and cardiovascular, respiratory, immunologic, neurologic, and reproductive effects. A number of studies have consistently found increases in cancer mortalities (all types combined) in the highest exposed workers with long latency periods, but the data on site-specific cancer are inconclusive. Among the dermal effects, chloracne is clearly a response associated with exposure to 2,3,7,8-TCDD and structurally related chemicals, but the threshold level of 2,3,7,8-TCDD at which it occurs has not been established. Moreover, there seems to be a great deal of innate human variability in the chloracne response between individuals (see Section 2.1.2). Hepatic changes observed in exposed populations include hepatomegaly, increased hepatic enzyme (GGT, AST, ALT) levels, induced hepatic microsomal activity (measured as increased D-glucaric acid excretion), alterations in porphyrin metabolism, and increases in serum lipid (cholesterol, triglycerides) levels. With the exception of long-lasting changes in GGT (Calvert et al. 1992; USAF 1991) and in serum cholesterol (USAF 1991) in some exposed groups, hepatic effects were transient and appeared to have been associated with acute exposure to high 2,3,7,8-TCDD concentrations. Few long-term thyroid effects were found in Ranch Hand veterans (USAF 1991), but a recent study of nursing infants suggests that ingestion of breast milk containing CDD and CDF levels somewhat higher than those reported in most general population studies, may alter thyroid function (these data are not conclusive because the measure thyroid hormone levels were within the normal range) (Koopman-Esseboom et al. 1994; Pluim et al. 1992). Slightly increased risk of diabetes and abnormal glucose tolerance tests have been reported in populations exposed to high 2,3,7,8-TCDD concentrations (Sweeney et al. 1992; USAF 1991). In the former study, however, age and body mass index, both known risk factors for diabetes, appear to have a greater influence than 2,3,7,8-TCDD level. Dose-related trends for deaths from cardiovascular disease and ischemic heart disease were observed in individuals exposed to CDDs during the BASF accident (Flesch-Janys et al. 1995). However, other studies found no relationship between 2,3,7,8-TCDD exposure and cardiovascular deaths (Bertazzi et al. 1989b) or other cardiovascular effects (Hoffman et al. 1986; Wolfe et al. 1985). A few case reports indicate that acute exposure to high 2,3,7,8-TCDD levels can produce respiratory irritation, but there is no indication that exposure to 2,3,7,8-TCDD produces chronic respiratory effects. Although there have been some reports of alterations in some immune end points in populations exposed to 2,3,7,8-TCDD, there has not been a consistent pattern, and the clinical significance of the effects is not totally clear. The overall evidence for neurologic effects suggests that although neurologic effects are reported to have occurred shortly after exposure in occupationally exposed individuals, even high exposure to 2,3,7,8-TCDD caused no long-term sequelae (Goetz et al. 1994; Sweeney et al. 1993). More recent data

suggests that exposure to 2,3,7,8-TCDD and related chemicals in humans during the pre- and neonatal periods may affect neurological development (Huisman et al. 1995a), but these data need to be interpreted cautiously because the neurological optimality score in infants was within the normal range and CDD/CDF levels may have only contributed a small amount to the variance in scores. Of the many reproductive end points studied in populations exposed to 2,3,7,8-TCDD, the available data provide suggestive evidence of altered sex ratios in children of exposed parents (Basharova 1996; Dimich-Ward et al. 1996; Mocarelli et al. 1996) and possibly alterations in reproductive hormone levels in males (Egeland et al. 1994) are associated with increased serum 2,3,7,8-TCDD levels.

Most of the toxicity studies of 2,3,7,8-TCDDs in animals have involved oral exposure, and numerous effects have been documented after short- and long-term exposure including lethality, and cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, body weight, immunologic, reproductive, and developmental effects. In addition, 2,3,7,8-TCDD is a potent carcinogen in various species, and produces tumors in multiple sites in rodents of both sexes. However, as shown in Table 2-2, these effects occurred at doses several orders of magnitude higher than estimates of background exposure for CDDs. The most reliable and consistent sign of 2,3,7,8-TCDD toxicity in experimental animals is weight loss or decreased weight gain in growing rodents. Animal responses to 2,3,7,8-TCDD exposure are species- and strain-dependent, although almost all responses can be induced in every species and strain if the appropriate dose is used. The animal data suggest that the most sensitive effects of 2,3,7,8-TCDD exposure are immunotoxicity, and reproductive and developmental toxicity.

In recent years considerable advances have been made regarding the mechanisms of toxicities of 2,3,7,8-TCDD and related chemicals, as well as the pharmacokinetics of dioxins in experimental animals. For CDDs, toxicity and toxicokinetics cannot be dealt with separately. Based on results from research in these fields, it has become apparent that the comparison of responses from animals to humans (or even between animal species) should be done on the basis of body-burden or target-tissue dose, rather than on the basis of administered dose. By doing so, species-specific toxicokinetic considerations such as dose-dependent distribution, the existence of tissue-specific sequestering chemical entities (i.e., CYP1A2), and body composition (i.e., percent fat) can be taken into account. A discussion of relationships between administered dose, body burden, and biological responses is presented below.

Issues relevant to children are explicitly discussed in Section 2.6, Children's Susceptibility, and Section 5.6, Exposures of Children.

Toxic Equivalency Factors (TEFs) and Toxic Equivalents (TEQs). Humans are exposed to complex mixtures of CDDs and other halogenated aromatic hydrocarbons such as CDFs and PCBs which are found in the environment (including food). The toxicological concerns resulting from exposure to these mixtures, as well as the gaps in available information with which to evaluate the potential risks from such exposures, led the EPA Chlorinated Dibenzo-p-dioxins/Chlorinated Dibenzofurans Technical Panel of the Risk Assessment Forum to recommend an interim method for assisting in estimating the risk from exposure to these mixtures that can be used until the data gaps are filled (Barnes 1991; EPA 1989e). Since for many of these chemicals very limited data on toxicity exist, TEFs were developed and validated in studies in animals (Eadon et al. 1986; Silkworth et al. 1989a; Viluksela et al. 1998a, 1998b).

The TEF approach involves assessment of the comparative effects of individual halogenated aromatic hydrocarbons congeners on various biological end points and derivation of TEFs based on the upper range of potency data for these effects The key assumptions unifying the diverse types of data that are considered in the derivation of TEFs are: that congeners exert toxicity through a common receptor-mediated mechanism, and that the effects of mixtures are additive (Safe 1990). The TEF approach compares the relative toxicity of individual congeners to that of 2,3,7,8-TCDD, which is the most extensively studied of the halogenated aromatic hydrocarbons that interact with the Ah receptor. The TEF for 2,3,7,8-TCDD is defined as unity; and TEFs for all other CDD congeners, CDFs, and dioxin-like PCBs are less than one, thus reflecting their lower toxic potency (see Kennedy et al. [1996] for an exception to this general rule). TEFs proposed earlier by EPA (1989) are presented in Table 2-11; recently revised values are presented in Table 2-12 (WHO 1998). The recent update also assigned a TEF of 1 to 1,2,3,7,8-PeCDD. The toxic potency of a mixture of congeners (i.e., the TEQ) is the sum of the products of the TEFs for each congener and its concentration in the mixture. Thus, TEQs represent 2,3,7,8-TCDD toxic equivalents for mixtures of CDDs, CDFs, and/or dioxin-like PCBs.

The TEF approach facilitates site-specific assessments that account for changes in congener composition due to differential environmental partitioning and transformation, as well as differences in congener profiles between sites and co-exposure to related halogenated aromatic hydrocarbons. The TEF approach, however, has several shortcomings. One problem is that very little data may be available for estimating the TEF and the available data are often from *in vitro* or single-exposure acute *in vivo* studies. Furthermore, there is a wide range in relative potency estimates derived from the literature. For example, Safe (1990) estimated 2,3,7,8-TCDD/1,2,3,4,7,8-HxCDD potency ratios of 33/1 for rat body weight loss, 12/1 for rat thymic atrophy, and 8/1 for AHH induction in cultured rat liver cells. One further problem is that

Table 2-11. Toxicity Equivalency Factors (TEFs) for Halogenated Hydrocarbons

CDFs	EPA current recommended values[a]	CDDs	EPA current recommended values[a]	PCBs	WHO/IPCS interim value[b]
monoCDFs	0	monoCDDs	0	3,3'4,4'-tetraCB	0.0005
diCDFs	0	diCDDs	0	3,3',4,4',5-pentaCB	0.1
triCDFs	0	triCDDs	0	2,3,3',4,4'-pentaCB	0.0001
2,3,7,8-tetraCDF	0.1	2,3,7,8-TCDD	1	2,3,4,4',5-pentaCB	0.0005
other tetraCDFs	0	other tetraCDDs	0	2,3',4,4',5-pentaCB	0.0001
1,2,3,7,8-pentaCDF	0.05	2,3,7,8-pentaCDD[c]	0.5	2',3,4,4',5-pentaCB	0.0001
2,3,4,7,8-pentaCDF	0.5	other pentaCDDs	0	3,3',4,4',5,5'-hexaCB	0.01
other pentaCDFs	0			2,3,3',4,4',5-hexaCB	0.0005
2,3,7,8-hexaCDF[c]	0.1	2,3,7,8-hexaCDD[c]	0.1	2,3,3',4,4',5'-hexaCB	0.0005
other hexaCDFs	0	other hexaCDDs	0	2,3',4,4',5,5'-hexaCB	0.00001
2,3,7,8-heptaCDF[c]	0.01	2,3,7,8-heptaCDD[c]	0.01	2,3,3',4,4',5,5'-heptaCB	0.0001
other heptaCDFs	0	other heptaCDDs	0	2,2',3,3',4,4',5,-heptaCB	0.0001
octaCDF	0.001	octaCDD	0.001	2,2',3,4,4',5,5'-heptaCB	0.00001

[a]Derived from EPA 1989e
[b]Derived from Ahlborg et al. 1994
[c]Any isomer that contains chlorine in the 2,3,7,8-positions

CDDs = chlorinated dibenzo-*p*-dioxins; CDFs = chlorinated dibenzofurans; PCBs = polychlorinated biphenyls; TCDD = tetrachlorodibenzo-*p*-dioxin

Table 2-12. World Health Organization (WHO)-TEFs for Humans, Mammals, Fish, and Birds

Compound	Humans/mammals	Fish[a]	Birds[a]
2,3,7,8-TCDD	1	1	1
1,2,3,7,8-PeCDD	1	1	1[f]
1,2,3,4,7,8-HxCDD	0.1[a]	0.5	0.05[f]
1,2,3,6,7,8-HxCDD	0.1[a]	0.01	0.01[f]
1,2,3,7,8,9-HxCDD	0.1[a]	0.01[e]	0.1[f]
1,2,3,4,6,7,8-HpCDD	0.01	0.001	<0.001[f]
OCDD	0.0001[a]	–	–
2,3,7,8-TCDF	0.1	0.05	1[f]
1,2,3,7,8-PeCDF	0.05	0.05	0.1[f]
2,3,4,7,8-PeCDF	0.5	0.5	1[f]
1,2,3,4,7,8-HxCDF	0.1	0.1	0.1[c,f]
1,2,3,6,7,8-HxCDF	0.1	0.1[c]	0.1[c,f]
1,2,3,7,8,9-HxCDF	0.1[a]	0.1[c,e]	0.1[c]
2,3,4,6,7,8-HxCDF	0.1[a]	0.1[c]	0.1[c]
1,2,3,4,6,7,8-HpCDF	0.01[a]	0.01[b]	0.01[b]
1,2,3,4,7,8,9-HpCDF	0.01[a]	0.01[b,e]	0.01[b]
OCDF	0.0001[a]	0.0001[b,e]	0.0001[b]
3,3',4,4'-TCB (81)	0.0001[a,b,c,e]	0.0005	0.1[e]
3,4,4',5-TCB (77)	0.0001	0.0001	0.05
3,3',4,4',5-PCB (126)	0.1	0.005	0.1
3,3',4,4',5,5'-HxCB (169)	0.01	0.00005	0.001
2,3,3',4,4'-PeCB (105)	0.0001	<0.000005	0.0001
2,3,4,4',5-PeCB (114)	0.0005[a,b,c,d]	<0.000005[b]	0.0001[g]
2,3',4,4',5-PeCB (118)	0.0001	<0.000005	0.00001
2,3,4,4',5-PeCB (123)	0.0001[a,c,d]	<0.000005[b]	0.00001[g]
2,3,3',4,4',5,-HxCB (156)	0.0005[b,c]	<0.000005	0.0001
2,3',4,4',5'-HxCB (157)	0.0005[b,c,d]	<0.000005[b,c]	0.0001
2,3',4,4'5,5'-HxCB (167)	0.00001[a,d]	<0.000005[b]	0.00001[g]
2,3,3',4,4'5,5'-HpCB (189)	0.0001[a,c]	<0.000005	0.00001[g]

[a] limited data set
[b] structural similarity
[c] quantitative structure activity relationships (QSAR) modeling prediction from CYP1A induction (monkey, pig, chicken, or fish)
[d] no new data from 1993 WHO review
[e] *in vitro* CYP1A induction
[f] *in vivo* CYP1A induction after *in ovo* exposure
[g] QSAR modeling prediction from class-specific TEFs

– = no TEF because of lack of data; HpCDD = heptachlorodibenzo-*p*-dioxin; HpCDF = heptachlorodibenzofuran; HxCB = hexachlorobiphenyl; HxCDD = hexachlorodibenzo-*p*-dioxin; HxCDF = hexachlorodibenzofuran; ND = not detected; OCDD = octachlorodibenzo-*p*-dioxin; OCDF = octachlorodibenzofuran; PeCDD = pentachlorodibenzo-*p*-dioxin; PeCDF = pentachlorodibenzofuran; TCB = tetrachlorobiphenyl; TCDD = tetrachlorodibenzo-*p*-dioxin; TCDF = tetrachlorodibenzofuran; TEF=Toxic equivalency factor.

Source: Van den Berg et al. 1998

differences in pharmacokinetics between two chemicals result in different estimates of the relative potency depending upon the exposure protocol (DeVito and Birnbaum 1995). These investigators demonstrated that published TEFs for 2,3,7,8-TCDD (TEF 1) and 2,3,7,8-TCDF (TEF 0.1) accurately estimated the relative potencies for liver EROD induction in female B6C3F_1 mice after 4 weeks of treatment, but failed to do so after 13 weeks of treatment. The inability to estimate relative potencies after the longer treatment duration was attributed to the difference in half-lives between the two compounds (2 days for 2,3,7,8-TCDF and 15 days for 2,3,7,8-TCDD). Steady-state levels of 2,3,7,8-TCDF were achieved within 4 weeks and, thus, EROD remained constant from 4 to 13 weeks. Steady-state levels of 2,3,7,8-TCDD were not attained within 4 weeks, which explained the increased hepatic EROD between 4 and 13 weeks. The results showed that TEFs for congeners with a short half-life may overestimate their potency and that the opposite may be true for congeners with a long half-life. Based on their results, DeVito and Birnbaum (1995) suggested that "present TEFs should be reevaluated to determine whether values have adequately incorporated pharmacokinetic differences between the test compound and 2,3,7,8-TCDD." In a more recent study, the same group of investigators compared the relative potencies for enzyme induction of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, OCDF, and 2,3,7,8-tetrabromodibenzo-*p*-dioxin (2,3,7,8-TBDD) in mice based on daily administered or final tissue dose following gavage dosing for 90 days (DeVito et al. 1997). The enzymes monitored were EROD (liver, lung, and skin) and ACOH (liver). After the 90-day administration period, the chemicals were assumed to be at or approaching steady-state conditions. Since ED_{50} values could not be estimated for all the congeners, the authors used an alternative method of comparison that fitted a function to the 2,3,7,8-TCDD dose-response data. The function was then used to predict the 2,3,7,8-TCDD equivalent dose of a chemical based on the enzymatic activity induced at a given dose of the test compound. A linear regression of the predicted dose of 2,3,7,8-TCDD and the actual congener dose provided the relative potency estimate. The results showed that, when based on administered dose, the relative potencies for the specific congeners did not vary substantially among tissues. However, for congeners with a much shorter half-life than 2,3,7,8-TCDD, the relative potencies increased for all enzymes when estimated from tissue concentrations. For example, for 2,3,7,8-TCDF the relative potency based on administered dose varied by less than a factor of 2 between endpoints, ranging from 0.0076 for skin EROD to 0.014 for ACOH. The relative potency increased by 4- to 14-fold when based on tissue dose and varied between tissues by a factor of 4, from 0.028 to 0.11. Because 2,3,7,8-TCDF is metabolized much faster than 2,3,7,8-TCDD, to achieve an equivalent tissue concentration of these chemicals, higher doses of 2,3,7,8-TCDF must be administered relative to 2,3,7,8-TCDD. Overall, the results confirmed their previous observations that differences in absorption and metabolism modulate the relative potency of this class of chemicals. DeVito et al. (1997)

suggested that it might be useful to derive two sets of TEF values, one used for estimating intake equivalents and the other for estimating tissue equivalents.

Viluksela et al. (1998a, 1998b) recently examined a wide range of endpoints in rats administered either a mixture of CDDs with a given TEQ or single CDD congeners at the same TEQ dose level as the mixture. The TEFs for the various congeners were derived from acute experiments. The dosing period was 13 weeks. The results showed effects of similar magnitude in response to administration of the CDD mixture or single CDD congeners. This supported the validity of the TEF method and the notion of additive toxicity for the CDDs evaluated. Moreover, the concentration ratios for the various congeners in the liver were very similar to the ratios at which the congeners were administered.

Neubert and coworkers (Neubert et al. 1992c) have also examined the issue of TEFs and proposed that a number of prerequisites need to be fulfilled in order to consider the TEF approach from a scientific point of view:

- The actions of the congeners must be strictly additive in the dose range to be evaluated.
- The organotropic manifestations in different species must be identical over the relevant dose ranges.
- Dose-response curves for various toxicological end points for a given congener must run parallel.
- The dose-response curves for a given toxicological end point must run parallel for the various congeners.
- For extrapolations between species, the kinetics must be identical, or differences have to be taken into consideration.
- With respect to a risk assessment relevant to humans, toxic or biological manifestations in the lower dose ranges are of special interest, and LD_{50} or ED_{50} values or effects induced by highly toxic dose are of minor importance.
- Effects to be expected at low exposures must be identical with those observed at the high doses studied.

After discussing each one of these seven points, Neubert et al. (1992c) concluded that the toxicological background for using the TEF approach for risk assessment must be increased considerably. A similar conclusion was reached by a scientific panel that examined the feasibility of developing a TEF approach that would be applicable to PCB mixtures (Barnes et al. 1991). In the case of PCBs, the study group concluded that “the application of TEF approach for PCBs would be less straightforward than it was in the case of chlorinated dibenzo-p-dioxins and dibenzofurans.”

In 1992, a group of scientists met in Belgium under the auspices of the European Environmental Research Organization to discuss the impact of CDDs, CDFs, and PCBs on human and environmental health with special emphasis on application of the TEF concept. The main conclusions, relevant to the TEF concept,

were that TEFs may be useful for risk management (i.e., quantitative estimation of Ah receptor-mediated toxic potential) of mixtures of CDDs, CDFs and the coplanar non-ortho and mono-ortho PCBs, but that the TEF concept is not applicable for the various toxic responses whose mechanisms do not involve the Ah receptor (Ahlborg et al. 1992, 1994).

The TEF approach in relation to cancer risk estimation has also been examined Rao and Unger (1995). First, the authors used the standard approach of multiplying TEF doses by the cancer slope factor for 2,3,7,8-TCDD to estimate lifetime incremental cancer risks for a mixture of CDDs and CDFs. This method was compared with a modified approach in which the TEF dose was adjusted for differences in the probability of formation of bound receptor-ligand complexes. Briefly, using algorithms from a competitive binding model, the fractions of Ah receptor bound to congeners were derived. This fraction was defined as competitive binding ratios (CBR) in mixtures and represents the maximum likelihood estimate for the formation of a congener-receptor bound complex in the presence of other competing ligands. Two distinct risk scenarios were used for comparison: (1) human adipose tissue residue data from the national human adipose tissue survey (Stanley et al. 1986) were used to generate potential lifetime incremental cancer risks, and (2) lifetime cancer risk was characterized for a potentially exposed population ingesting contaminated carp. In the modified TEF approach, CBR values for individual congeners computed from the competitive binding algorithms were used to derive the tissue concentrations. The main findings of this analysis were that TEF doses calculated by using the model algorithms were lower than the combined TEF dose for all congeners estimated by the TEF method without considering the competitive binding. In addition, the combined incremental cancer risks for all congeners were generally lower when model algorithms were used in the dose-response analysis. Also, the standard TEF method tended to overestimate the risks of higher congeners with low toxicity and underestimated the risk of more toxic congeners.

One further concern regarding the use of TEQs for risk assessment is the fact that the human diet also contains Ah receptor agonists, such as indole-3-carbinol and related compounds in vegetables, polynuclear aromatic hydrocarbons (PAHs), aromatic amines formed during cooking. These natural Ah receptor agonists elicit responses in humans that are consistent with a receptor-mediated pathway, but the response-specific potencies of natural Ah receptor versus xenodioxins are unknown. Therefore, a TEF/TEQ approach based solely on intake of xenodioxins does not take into account the background of natural dioxins that may influence responses associated with persistent low-level occupation of the Ah receptor (see Safe 1998a, 1998b for review on this issue).

Minimal Risk Levels for 2,3,7,8-TCDD

It is ATSDR's policy (see Appendix B) to use health guidance values (i.e., MRLs, EMEGs) derived for 2,3,7,8-TCDD for other dioxin-like compounds, expressed in total TEQs.

Inhalation MRLs

MRLs were not derived for inhalation exposure.

Oral MRLs

- An MRL of 0.0002 (2×10^{-4}) µg/kg/day has been derived for acute-duration oral exposure (14 days or less) to 2,3,7,8-TCDD.

The acute duration oral MRL was based on a NOAEL of 0.005 µg/kg and a LOAEL of 0.01 µg/kg for immunological effects in female mice (Burleson et al. 1996). In this study, groups of 20 female B6C3F_1 mice were administered a single gavage dose of 0, 0.001, 0.005, 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD in corn oil. Seven days after 2,3,7,8-TCDD exposure, the mice were infected intranasally with influenza A/Hong Kong/8/68 (H3N2) virus diluted at 10^{-48}, 10^{-50}, 10^{-52}, or 10^{-54}. In a separate experiment, groups of 18 female mice received a single gavage dose of 0, 0.001, 0.01, or 0.1 µg/kg 2,3,7,8-TCDD and were infected 7 days later with influenza A virus at a dose not known to cause mortality (10^{-54} and 10^{-58}) or were sham-infected. Body weight, thymus weight, and wet lung weights were measured 3, 9, or 12 days postinfection. Pulmonary virus titers were determined in groups of 72 mice exposed to 0, 0.001, 0.01, or 0.01 µg/kg 2,3,7,8-TCDD and infected with influenza A virus seven days later. For the virus titer study, groups of mice were killed 2 hours, 1, 4, 6, 7, 8, 9, 10, and 11 days post-infection.

Statistically significant increases in mortality were observed in the influenza A infected mice exposed to 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD. However, no between group differences in mortality were observed at these 2,3,7,8-TCDD dosages. Mortality in mice receiving 0.001 or 0.005 µg/kg did not significantly differ from the mortality in the control group. Exposure to 2,3,7,8-TCDD did not enhance the increase in relative lung weight normally seen in mice infected with influenza A virus. As compared to controls, no significant alterations in thymus weights were observed in 2,3,7,8-TCDD-exposed mice sham-infected or those infected with influenza A virus. 2,3,7,8-TCDD exposure did not result in a significant increase in viral titers in the lung, as compared to titers from the control group. The authors noted that the

lack of dose-response in mortality and the lack of effect on the relative lung weight, thymus weight, and viral titers suggest that 2,3,7,8-TCDD may be exerting an effect via an indirect mechanism such as through an effect on cytokines. The 0.005 µg/kg dose was considered a NOAEL for immunotoxicity. As described in the footnote to Table 2-2, an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) and modifying factor of 0.7 (to adjust for the difference in higher bioavailability of 2,3,7,8-TCDD from an oil gavage vehicle than from food) were used to derive the MRL from the NOAEL value.

- An MRL of 0.00002 (2×10^{-5}) µg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 2,3,7,8-TCDD.

The intermediate-duration oral MRL was based on a NOAEL of 0.0007 µg/kg/day for immunological effects in Hartley guinea pigs fed 2,3,7,8-TCDD in the diet for 90 days (DeCaprio et al. 1986). In that study, groups of weanling Hartley guinea pigs (10 per sex) were administered a diet that provided an average of 0.0001, 0.0007, 0.005, or 0.028 µg 2,3,7,8-TCDD/kg/day. This corresponds to 2, 10, 76, and 430 ppt 2,3,7,8-TCDD in the food. A control group was fed a diet without added 2,3,7,8-TCDD. The recovery following treatment was studied in groups of 10 guinea pigs fed a diet containing 430 ppt 2,3,7,8-TCDD for 11, 21, or 35 days and allowed to recover for 79, 69, or 55 additional days, respectively. The highest dietary level of 2,3,7,8-TCDD caused net body weight loss and mortality. Four males and four females died, and additional animals had to be sacrificed due to poor health. Food consumption was significantly reduced in the highest-dose group only. Body weight gain in the 0.0007 and 0.005 µg/kg/day male groups was reduced by 9 and 20%, respectively. In the corresponding female groups, body weight gain was reduced by 6 and 15%. Gross lesions were observed only in the highest-dose group and included thymic atrophy, depletion of body fat, and liver enlargement. Significant changes in organ weights included a decrease in absolute kidney weight and in absolute and relative thymus weight in males dosed with 0.005 µg/kg/day, increase in relative liver weight in males and females at the 0.005 µg/kg/day level, and increase in relative brain weight in males at this same dose level. Organ weights from high-dose animals were not monitored. Administration of 2,3,7,8-TCDD did not cause any significant hematological effect (blood was not collected from the highest-dose group). In the 0.005 µg/kg/day groups, serum ALT was significantly reduced in females, and triglycerides were elevated in males. No other significant changes in clinical chemistries were observed. Treatment-related histological alterations were observed only in the two higher-dose groups and consisted of hepatocellular cytoplasmic inclusion bodies and atrophy of the thymic cortex. In the recovery study there was 10% mortality in the groups treated for 11 and 21 days, and 70% mortality in the group treated for 35 days. Surviving animals in all groups exhibited significantly

reduced body weight gain. The 0.0007 µg/kg/day dose represents a NOAEL for decreased thymus weight, and the 0.005 µg/kg/day dose is a LOAEL. As described in the footnote to Table 2-2, an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) was used to derive the MRL from the NOAEL.

- An MRL of 0.000001 (1×10^{-6}) µg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to 2,3,7,8-TCDD.

The chronic-duration oral MRL is based on a LOAEL of 0.00012 µg/kg/day for developmental toxicity in rhesus monkeys (Schantz et al. 1992). In this study, groups of 8 female rhesus monkeys were fed a diet containing 0, 5, or 25 ppt 2,3,7,8-TCDD for a total of 16.2 months (the results of the neurodevelopmental portion of this study were published in papers by Bowman et al. [1989a], Schantz and Bowman [1989], Schantz et al. [1992]). After 7 months of exposure, the monkeys were mated with unexposed males. (Only 1 monkey in the 25 ppt group delivered a viable offspring; this offspring was not studied behaviorally.) The monkeys were fed the 2,3,7,8-TCDD diet throughout the mating period, gestation, and lactation. When the offspring (3 males and 3 females per exposure group) were 8.6 months of age, they were placed in 3 peer groups of 4 monkeys and allowed to play for 1.5 hours without interference. The peer groups consisted of two 2,3,7,8-TCDD-exposed monkeys and two control monkeys. Behavioral patterns (social interactions and other behaviors such as vocalization, locomotion, self-directed behavior, and environmental exploration) were monitored 4 days a week for 9 weeks. No overt signs of toxicity were observed in the mothers or offspring, and birth weights and growth were not adversely affected by 2,3,7,8-TCDD exposure. Significant alterations were observed in play behavior, displacement, and self-directed behavior in the 2,3,7,8-TCDD-exposed offspring. 2,3,7,8-TCDD-exposed monkeys tended to initiate more rough-tumble play bouts and retreated less from play bouts than controls, were less often displaced from preferred positions in the playroom than the controls, and engaged in more self-directed behavior than controls. No other significant alterations in behavior or alterations in reflex development, visual exploration, locomotor activity, or fine motor control were found (Bowman et al. 1989a). In tests of cognitive function, object learning was significantly impaired, but no effect on spatial learning was observed (Schantz and Bowman 1989). As described in the footnote to Table 2-2, an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) was used to derive the MRL.

It should be also noted that 10 years after termination of 2,3,7,8-TCDD exposure in the Schantz et al. (1992) study, Rier et al. (1993) reported a dose-related increase in the incidence and severity of

endometriosis in these same rhesus monkeys. Rier et al. (1993) identified a less serious LOAEL of 5 ppt (0.00012 µg/kg/day) for moderate endometriosis. However, monkeys appear to be more susceptible to endometriosis, based on a background incidence of endometriosis in monkeys of 30% (Rier et al. 1993) compared to a background incidence of 10% in humans (Wheeler 1992). Thus, derivation of a chronic oral MRL based on endometriosis would necessitate using an uncertainty factor of less than 1 (or at most, 1) to account for the increased sensitivity of monkeys to endometriosis as compared to humans. If the Rier et al. (1993) study were used to calculate an oral MRL, the LOAEL of 0.00012 µg/kg/day would be divided by an uncertainty factor of 100 (10 to extrapolate from a LOAEL, 10 for human variability and 1 for interspecies differences). This would result in a computed MRL essentially the same as the chronic oral MRL of 1 pg/kg/day based on developmental toxicity as described in the preceding paragraph. Moreover, (1) the clinical history for these rhesus monkeys during the 10-year period between the Schantz et al. (1992) study and examination by Rier et al. (1993) is unknown (not reported); (2) Boyd et al. (1995) did not find an association between exposure to CDDs, CDFs, or PCBs and endometriosis in a clinical study in women; and (3) the EPA (1997) concluded that "the evidence for supporting the hypothesis that CDDs and PCBs are causally related to human endometriosis via an endocrine-disruption mechanism is very weak." So, even though there is information to indicate that endometriosis may also be a sensitive toxicological end point for 2,3,7,8-TCDD exposure, the developmental end point (altered social behavior) reported in the Schantz et al. (1992) study was determined to be the most appropriate end point for derivation of an MRL for chronic oral 2,3,7,8-TCDD exposure.

Comparison of Estimated Body Burdens Associated with Effects in Experimental Animals and Humans. Estimated average body burdens of 2,3,7,8-TCDD in human populations in which various health effects of 2,3,7,8-TCDD are suspected range from 31 to 6,600 ng/kg (estimated body burdens at the time of exposure termination). See Table 2-1 for more information. The human body burden expected in populations exposed to background environmental levels of 2,3,7,8-TCDD has been estimated to be 1 ng TCDD/kg body weight (DeVito et al. 1995; Orban et al. 1994). This would suggest that effects of 2,3,7,8-TCDD in humans may occur at body burdens that are 30 to 6,600 times greater than background burdens for 2,3,7,8-TCDD.

The similarities in response of humans and experimental animals to similar body burdens of CDDs and related chemicals (Table 2-10), along with our understanding of common mechanisms of actions of CDDs in humans and experimental animals lends support to both the relevance of experimental animal toxicology to humans and the use of experimental animal data for establishing MRLs (see Section 2.4.3 for more

information on the animal-to-human extrapolations). Acute, intermediate and chronic MRLs for 2,3,7,8-TCDD were derived from experimental animal studies that identified the highest NOAELs or lowest LOAELs for the respective exposure-duration category (Table 2-2). The MRLs, and the NOAELs and LOAELs on which they are based, have been converted to their corresponding equivalent body burdens and are compared to background 2,3,7,8-TCDD body burdens in humans and body burdens associated with adverse health effects (Table 2-13). This comparison shows that the NOAELs for acute, intermediate, and LOAEL for chronic exposure to 2,3,7,8-TCDD in experimental animals are generally below the low end of the 31–6,600 ng TCDD/kg of body weight range of body burdens that is suspected to be adverse to humans based on the epidemiologic evidence. Body burdens that correspond to the MRLs are 2-6 times lower than the estimated background body burden in humans, suggesting that adverse health effects are unlikely in humans exposed to background levels of 2,3,7,8-TCDD. However, because of the magnitude of uncertainty in dose-response relationships for 2,3,7,8-TCDD, the possibility that current background exposures may be sufficient to contribute to a risk of adverse health effects in human populations cannot be completely excluded.

Death. Information regarding mortality in humans after exposure to CDDs is limited to epidemiological studies in populations exposed occupationally or environmentally (Bertazzi et al. 1989b; Cook et al. 1986, 1987b; Fingerhut et al. 1991; Ott et al. 1980, 1987; Pesatori et al. 1998; Thiess et al. 1982; Vena et al. 1998; Wolfe et al. 1985; Zack and Suskind 1980; Zober et al. 1990). These studies did not find a significant increase in the overall mortality rate in populations exposed to 2,3,7,8-TCDD or other CDD congeners for acute or chronic durations. However, several studies did find significant increases in cause-specific mortality (i.e., cancer and cardiovascular disease). These increases in cause-specific mortality are discussed under the specific effect.

Several studies provided data regarding lethality following CDDs exposure in animals. Oral LD_{50} values for 2,3,7,8-TCDD were calculated in rats (NTP 1982b; Schwetz et al. 1973; Walden and Schiller 1985), minks (Hochstein et al. 1988), rabbits (Schwetz et al. 1973), guinea pigs (McConnell et al. 1984; Schwetz et al. 1973), and hamsters (Henck et al. 1981) following gavage doses in corn oil or corn oil:acetone vehicle. Doses that produced death were in the µg/kg range. Differences in the susceptibility to the lethality of 2,3,7,8-TCDD were observed not only among different species, but also among different strains

Table 2-13. Estimated Body Burdens of 2,3,7,8-TCDD That Correspond to MRLs

Duration	Risk or effect level	Exposure (ng/kg/day)	Body burden (Cb)[a] (ng/kg bw)
Acute	MRL	0.2	0.16[b]
	NOAEL	5	4[b]
	LOAEL	10	8[b]
Intermediate	MRL	0.02	0.66[c]
	NOAEL	0.7	23[c]
	LOAEL	5	164[c]
Chronic	MRL	0.001 (maternal dose)	0.26 (peak maternal)[d] 0.76 (offspring at weaning)[e]
	LOAEL	0.12 (maternal dose)	32 (peak maternal)[d] 68 (offspring at weaning)
Human health effects	—	—	31–6,600[f]
Human background	—	—	1[g]

[a] Estimated as follows: Cb = (I·a·f)/k, f = 1-(e^{-kt}); where, C_b is the 2,3,7,8-TCDD body burden (ng/kg bw), I is 2,3,7,8-TCDD intake (ng/kg-day), a is the gastrointestinal absorption fraction, f is the fraction of steady-state body burden, k is the whole body elimination rate constant for 2,3,7,8-TCDD (day^{-1}, $ln2/t_{1/2}$), and t is the exposure duration (day)

[b] Assumed parameter values for mice in Burleson et al. (1996) study: a = 0.8 (Curtis et al. 1990), $t_{1/2}$ = 11 days (Birnbaum 1986)

[c] Assumed parameter values for guinea pigs in DeCaprio et al. (1986) study: a = 0.5 (Van den Berg et al. 1994), $t_{1/2}$ = 94 days (Olson 1986)

[d] Assumed parameter values for monkeys in Schantz et al. (1992) study: a = 0.8 (value for rats from Van den Berg et al. 1994), $t_{1/2}$ = 391 days (Bowman et al. 1989b)

[e] At 5 months (weaning), the reported mean 2,3,7,8-TCDD concentration of adipose tissue in offspring was 377 ng/kg; this is equivalent to approximately 68 ng/kg bw, assuming that adipose tissue was 72% lipid and 13% of the body weight was lipid (Bowman et al. 1989b) ([377 x 0.13]/0.72=68). Assuming a reported linear regression relating 2,3,7,8-TCDD in adipose at weaning and maternal 2,3,7,8-TCDD in adipose at parturition, (Bowman et al. 1989b), 377 ng/kg adipose in offspring is equivalent to 84 ng/kg maternal adipose, or 17 ng/kg bw, assuming maternal adipose is 72% lipid and maternal body weight is 15% lipid (Bowman et al. 1989b). At the MRL exposure level, the 2,3,7,8-TCDD body burden in the offspring was calculated by dividing the 68 ng/kg body burden by the uncertainty factor used to calculate the chronic MRL (90).

[f] From Table 2-1

[g] From Orban et al. (1994) and DeVito et al. (1995)

within the same species, and even in the same strain of rat bred in different laboratories (Walden and Schiller 1985). The use of rats of different ages may have played a role in the interlaboratory differences in susceptibility between rats of the same strain. Toxicity results from acute- and intermediate-duration categories indicated that the guinea pig is the most sensitive species to 2,3,7,8-TCDD toxicity leading to death (DeCaprio et al. 1986; McConnell et al. 1984; Schwetz et al. 1973; Vos et al. 1973), and that the hamster is the most resistant (Hanberg et al. 1989; Henck et al. 1981). Experiments with mice that were injected with 2,3,7,8-TCDD intraperitoneally showed that the C57BL/6J mice responsive to 2,3,7,8-TCDD-induced toxicity were twice as sensitive to 2,3,7,8-TCDD-induced lethality as the less-responsive DBA/2J strains (Gasiewicz et al. 1983a). Increased mortality was also recorded in mice following intermediate-duration dermal exposure to 2,3,7,8-TCDD (NTP 1982a).

Toxicity data in animals indicated that similar effects occur after exposure to CDDs by oral, dermal, or parenteral routes. Toxicokinetic data in mice showed that 2,3,7,8-TCDD hepatic levels were similar following oral, intraperitoneal, and subcutaneous exposure (Nau and Bass 1981). However, recent data in rats showed that intratracheal administration of a 2,3,7,8-TCDD dose resulted in a relatively higher accumulation of 2,3,7,8-TCDD in the liver than after oral administration of the same dose (Diliberto et al. 1996). Intraperitoneal administration of 2,3,7,8-TCDD was less toxic than oral dosing in acute-exposure experiments with hamsters (Olson et al. 1980a).

Following acute oral exposure to 2,3,7,8-TCDD, death occurred within 6–42 days depending on the dose and species tested, indicating a delayed type of toxicity. Death was usually preceded by significant weight loss in all duration categories. However, weight loss did not appear to be the only cause of death. A total parenteral nutrition fluid given to 2,3,7,8-TCDD-exposed rats and guinea pigs protected the animals against wasting syndrome, but not against 2,3,7,8-TCDD-induced lethality (Gasiewicz et al. 1980; Lu et al. 1986). Specifically, biochemical changes indicative of severe liver damage were found in moribund rats.

2,3,7,8-TCDD was found not only to be more toxic than its isomer 1,2,3,4-TCDD (Courtney 1976) but also more toxic than any other congener tested (2,7-DCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD) (Courtney 1976; NCI/NTP 1980; NTP 1982b; Viluksela et al. 1994, 1998a). LD_{50} values for acute oral exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD derived for rats and mice (NCI/NTP 1980) were higher by more than 2 orders of

magnitude than LD_{50} values for 2,3,7,8-TCDD. However, 1,2,3,4,6,7,8-OCDD and 2,7-DCDD did not cause death in mice even at doses as high as 4,000 and 2,000 mg/kg, respectively.

Systemic Effects.

Respiratory Effects. No exposure-related respiratory effects were found in a group of Air Force Vietnam veterans exposed to 2,3,7,8-TCDD during aerial spraying studied sometime after exposure (Wolfe et al. 1985). No respiratory effects clearly attributable to 2,3,7,8-TCDD have been found in workers potentially exposed (Calvert et al. 1991). In rhesus monkeys, intermediate-duration exposure to a lethal oral dose of 2,3,7,8-TCDD caused nose bleeding (McNulty 1984), hemorrhage, and hyperplasia of the bronchial epithelium (Allen et al. 1977). Bronchiolar adenomatoid changes were seen in mice chronically exposed dermally (NTP 1982a). Furthermore, hyperplastic changes in the lungs were recorded in rats exposed orally to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980). However, mostly negative results were obtained in other oral studies in animals regardless of duration of exposure (Holsapple et al. 1986b; Kociba et al. 1978a; NCI/NTP 1979a; NTP 1982a, 1982b). The relevance of the animal findings to human health is unclear. Intense acute exposure to 2,3,7,8-TCDD can produce respiratory irritation, but the findings from controlled epidemiologic studies do not support an association between 2,3,7,8-TCDD exposure and chronic respiratory disease. It should be noted, however, that chronic bronchitis and related effects were observed in many Yusho and Yu-Cheng patients, who were exposed to the structurally related CDFs (ATSDR 1994).

Cardiovascular Effects. While some studies have found an association between CDD exposure and cardiovascular disease, most studies have not found a clear association between exposure to 2,3,7,8-TCDD and diseases of the heart and circulatory system (Bond et al. 1983; Calvert et al. 1998; Hoffman et al. 1986; Moses et al. 1984; Reggiani 1980; Suskind and Hertzberg 1984; Wolfe et al. 1985). However, human studies have suffered from limitations such as examination of the cohorts after exposure has ended, thus allowing for tissue repair to occur; lack of good exposure data; and inability to examine the relationship between serum 2,3,7,8-TCDD levels and cardiovascular disease in most studies. In the Ranch Hand study (USAF 1991), a weak association was found between decreased mean diastolic blood pressure, cardiac arrhythmias, and decreases in peripheral pulses and exposure to 2,3,7,8-TCDD. Bertazzi et al. (1989b) and Pesatori et al. (1998) found increases in deaths from ischemic heart disease and cardiovascular disease in men and chronic rheumatic heart disease in women in the 10-year period following the Seveso accident. However, the authors attributed these findings to post-accident stress rather than the 2,3,7,8-TCDD

exposure. In workers exposed occupationally to 2,3,7,8-TCDD and other CDD congeners at the Boehringer Hamburg plant, a statistically significant trend for increased risk of cardiovascular disease and ischemic heart disease mortalities with increasing serum lipid levels of 2,3,7,8-TCDD or TEQ (CDDs and CDFs) was found (Flesch-Janys et al. 1995). An international study of more than 20,000 workers followed from 1939 to 1992 found an increased risk for death from cardiovascular disease, especially ischemic heart disease, among exposed workers, but the authors did not rule out the influence of risk factors such as cigarette smoking, high fat diet, obesity, physical inactivity, and serum lipids (Vena et al. 1998).

Experiments in animals demonstrated that exposure to relatively high doses of 2,3,7,8-TCDD can cause various pathophysiological effects. Acute oral exposure of rats increased the basal tension of the left cardiac atria (Kelling et al. 1987) or decreased the basal rate for spontaneous beating, depending on the dose used (Hermansky et al. 1988; Kelling et al. 1987). Reduced blood pressure and increased myocardial peroxidase activity were also recorded. All of the effects on the heart in these two studies were attributed to a hypothyroid condition caused by near-lethal doses (Hermansky et al. 1988). Other studies have suggested a direct effect of 2,3,7,8-TCDD on cardiac muscle, as for example an intraperitoneal injection of 2,3,7,8-TCDD to guinea pigs reduced the contractive responsiveness of isolated myocardium (Brewster et al. 1987; Canga et al. 1988).

Reports of histological findings are few. Myocardial degenerative changes were reported in rats after chronic oral exposure to a lethal dose of 2,3,7,8-TCDD (Kociba et al. 1978a), and hemorrhages were reported in monkeys after intermediate-duration dietary exposure to near-lethal doses (Allen et al. 1977). However, most studies did not find any histopathological changes in rats and mice following chronic oral exposure to 2,3,7,8-TCDD (NTP 1982b), 2,7-DCDD (NCI/NTP 1979a), or a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980). Similarly, no changes were reported after chronic dermal exposure of mice to 2,3,7,8-TCDD (NTP 1982a). There is no conclusive evidence that the cardiovascular system is a target for 2,3,7,8-TCDD toxicity.

Gastrointestinal Effects. Limited information is available regarding gastrointestinal effects of 2,3,7,8-TCDD in humans. Earlier studies of individuals with exposure to substances contaminated with 2,3,7,8-TCDD found significant elevations in self-reported ulcers (Bond et al. 1983; Suskind and Hertzberg 1984), but a study of Vietnam veterans (USAF 1991) failed to find such effect. A more recent cross-sectional medical study of workers employed more than 15 years earlier in the production of

2,3,7,8-TCDD-contaminated chemicals found no association between 2,3,7,8-TCDD exposure (body burden) and gastrointestinal disease (Calvert et al. 1992).

Only a few of the numerous animal studies found any effects. Gastrointestinal ulcerations were reported in minks after an acute oral exposure to a lethal dose of 2,3,7,8-TCDD (Hochstein et al. 1988), and hemorrhages were reported in rats following chronic exposure (Van Miller et al. 1977). Ileitis and peritonitis were observed in hamsters receiving a single lethal dose of 2,3,7,8-TCDD (Olson et al. 1980a). A trophic effect on the antral mucosa was found in 2,3,7,8-TCDD treated rats, in contrast to atrophy found in pair-fed control animals (Theobald et al. 1991). Although these authors attempted to relate the mechanism of action to hormonal effects, a definitive mechanism was not established. Changes progressing from epithelial hyperplasia and metaplasia of gastric mucosa to stomach ulcerations were observed in rhesus monkeys with prolonged oral exposure (Allen et al. 1977; McConnell et al. 1978a; McNulty 1984). These data indicate that primates are particularly sensitive to 2,3,7,8-TCDD-induced gastrointestinal toxicity; however, the effects are seen at doses which caused severe toxicity at multiple sites. In contrast, most studies in rodents did not find any gastrointestinal effects after oral or dermal exposure to 2,3,7,8-TCDD (Christian et al. 1986a; Henck et al. 1981; Kociba et al. 1978a; NTP 1982a, 1982b), or after oral exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980) and 2,7-DCDD (NCI/NTP 1979a). The available information suggests that the gastrointestinal tract is not a target for 2,3,7,8-TCDD toxicity in humans.

Hematological Effects. Limited human data were located regarding hematological effects following exposure to CDDs. Increases in leukocyte and platelet counts were reported in Vietnam veterans involved in Operation Ranch Hand (USAF 1991), which suggested the presence of a low-level, chronic inflammatory response related to higher levels of 2,3,7,8-TCDD exposure. Increased prevalence of high white blood cell counts was found in a population exposed to 2,3,7,8-TCDD in the environment, but the increase was not of clinical importance (Hoffman et al. 1986), and other epidemiological studies reported negative results (Stehr et al. 1986; Wolfe et al. 1985).

Increased packed-cell volume was found in guinea pigs following a single intraperitoneal injection of 2,3,7,8-TCDD; however, this was considered to be secondary to progressive dehydration of exposed animals with decreased water consumption (Gasiewicz and Neal 1979). Several studies in animals reported hematological effects after intermediate-duration exposure to 2,3,7,8-TCDD. Among the effects observed were reduced leukocytes in guinea pigs at 0.001 µg/kg/day (Vos et al. 1973), thrombocytopenia and

hemoconcentration in rats at 0.8–1 µg/kg/day (Viluksela et al. 1994; Zinkl et al. 1973), and anemia and bone marrow hypoplasia in rhesus monkeys at 0.1 µg/kg/day (McNulty 1984). Reduced erythrocytes was reported in rats chronically exposed to 0.1 µg 2,3,7,8-TCDD/kg/day in the feed (Kociba et al. 1978a).

Splenic changes include reduced germinal centers after acute (Christian et al. 1986a) and splenic atrophy after chronic (Van Miller et al. 1977) oral exposures in rats. Furthermore, splenic hyperplasia was found in rats orally exposed to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD for an intermediate duration (NCI/NTP 1980). Whether or not the splenic changes were secondary to hematopoietic effects is unclear.

No hematological effects were found after acute oral exposure in minks (Hochstein et al. 1988) and mice (Holsapple et al. 1986a), intermediate oral exposure in guinea pigs (DeCaprio et al. 1986), chronic oral exposure in rats and mice (NTP 1982a; Oughton et al. 1995), chronic dermal exposure in mice (NTP 1982a), and acute intraperitoneal exposure in rats (Mason and Safe 1986a). Similarly, no effects were reported in rodents exposed chronically to 2,7-DCDD (NCI/NTP 1979a) or a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980) by the oral route, but thrombocytopenia was reported in male Sprague-Dawley rats exposed for 13 weeks to 1,2,3,4,6,7,8-HpCDD (Viluksela et al. 1994). Decreased hematocrit and reduced platelet counts were reported in rats administered 1,2,3,7,8-PeCDD or 1,2,3,4,7,8-HxCDD for 13 weeks at dose levels that caused lethality (Viluksela et al. 1998a).

No clear picture regarding hematologic effects of 2,3,7,8-TCDD emerges from the studies in animals. From the limited data, it appears, however, that mice are less sensitive than other species. The relevance of the findings in animals to human health is difficult to ascertain.

Musculoskeletal Effects. No relevant information was located regarding musculoskeletal effects in humans exposed to CDDs. However, evidence from case reports in the Yu-Cheng incident (which involved oral exposure to the structurally related CDFs and PCBs) indicate that musculoskeletal effects may occur after oral exposure to CDDs. Guo et al. (1994) reported that Yu-Cheng children were smaller and had less total lean mass and soft-tissue mass compared to matched control subjects. Hemorrhages in the musculoskeletal system of monkeys were observed following an oral intermediate-duration exposure to 2,3,7,8-TCDD (Allen et al. 1977). However, monkeys in this experiment were in terminal stages, and hemorrhages were found in several other systems. There is no evidence that would indicate that the musculoskeletal system is a target for 2,3,7,8-TCDD toxicity in humans or in animals.

Hepatic Effects. Exposure to 2,3,7,8-TCDD induces liver microsomal enzymes in both humans and animals, regardless of the route or duration of exposure. Increased urinary δ-glucaric acid (UGA) excretion, an indirect index of enzyme induction, was found in children with chloracne living in the Seveso area following the 1976 industrial accident (Ideo et al. 1982). Biochemical changes (increased cholesterol and bilirubin levels, induced GGT and ALT activities) indicated liver effects in exposed humans (Hoffman et al. 1986; Mocarelli et al. 1986). Biochemical changes indicative of a subclinical effect on lipid metabolism were found in Vietnam veterans involved in Operation Ranch Hand (USAF 1991). Biochemical examinations found disorders in the metabolism of porphyrins, lipids, carbohydrates, and plasma proteins in workers exposed to 2,3,7,8-TCDD during the manufacture of herbicides (Jirasek et al. 1976; Pazderova-Vejlupkova et al. 1981). In addition, histopathological changes (steatosis, fibrosis) were also documented. A more recent and better-designed study of workers employed at 2 chemical plants in the manufacture of sodium trichlorophenol and its more than 15 years earlier derivatives found no evidence of an elevated risk for long-term clinical hepatic disease (Calvert et al. 1992). Exposure was assessed by measuring lipid-adjusted serum 2,3,7,8-TCDD levels, and exposed workers had serum 2,3,7,8-TCDD levels significantly higher than unexposed controls. The negative findings, however, are not necessarily inconsistent with results from earlier studies, but suggest that hepatic effects observed in humans immediately after exposure probably resolve with time. A follow-up study of the same cohort found a positive association between serum 2,3,7,8-TCDD levels and the concentration of triglycerides and a negative correlation with HDL cholesterol; these associations were small when compared with the influence of many other factors (Calvert et al. 1996).

Studies in animals have shown that exposure to 2,3,7,8-TCDD can induce hepatotoxicity in several species administered the chemical by various exposure routes for several exposure durations. The severity of the lesion is dependent not only on the species, but also on the strain. In general, it appears that rats exhibit more signs of hepatotoxicity than guinea pigs and hamsters. Histological alterations of the liver are common findings observed in animals exposed to 2,3,7,8-TCDD. These effects have been reported after acute exposure in rats (Christian et al. 1986; Hermansky et al. 1988), mice (Greig 1984; Greig et al. 1987; Kelling et al. 1985), and guinea pigs (Turner and Collins 1983); after intermediate-duration exposure in rats (NTP 1982b; Van Miller et al. 1977), mice (Thigpen et al. 1975), guinea pigs (DeCaprio et al. 1986), and monkeys (Allen et al. 1977; McNulty 1984); and after chronic exposure in rats (Kociba et al. 1978a). Hepatic lesions in rats are characterized by degenerative and necrotic lesions with the appearance of mononuclear cell infiltration, multinucleated giant hepatocytes, and increased number of mitotic figures and intracytoplasmic lipid droplets. Markers of hepatic damage such as serum ALT and AST activities usually

increase in animals that exhibit altered liver histology (Greig 1984; Rosenthal et al. 1989; Smith et al. 1981). DBA/2J mice developed hepatic necrosis and inflammation without fatty changes after acute intraperitoneal exposure to 2,3,7,8-TCDD (Shen et al. 1991). Only slight lipid accumulation was found after exposure to a high dose (600 µg/kg). In contrast, severe fatty changes were observed in C57BL/6J mice, indicating that the steatitic effect may depend on the Ah locus. Histological lesions may be severe enough to be a contributing factor in death. Dose-related increases in intracellular and paracellular permeability of the biliary tree was observed in rats administered ip doses of 2,3,7,8-TCDD (Davidson and Fujimoto 1987).

2,3,7,8-TCDD has been found to be porphyrogenic in both rats and mice (Cantoni et al. 1981; Goldstein et al. 1977, 1982; Jones and Sweeney 1977, 1980). The mechanism of induction of porphyria is not known. 2,3,7,8-TCDD is a potent inducer of the initial and rate-limiting enzyme involved in heme synthesis, ALA-synthetase, but no increased activity was seen in mice which exhibited porphyria after treatment with 2,3,7,8-TCDD for 11 weeks (Jones and Sweeney 1980). A more likely explanation is that the primary event in 2,3,7,8-TCDD-induced porphyria is inhibition of hepatic porphyrinogen decarboxylase (Jones and Sweeney 1980). Crossbreeding experiments have shown that porphyrinuria was inherited together with AHH inducibility (Jones and Sweeney 1980), indicating that the Ah locus is involved in the porphyrogenic response to 2,3,7,8-TCDD.

Enzyme induction is one of the most sensitive responses to 2,3,7,8-TCDD exposure, and has been one of the most extensively studied biochemical responses produced by 2,3,7,8-TCDD. The MFO system is the most thoroughly investigated, and AHH and EROD (CYP1A1 markers) and acetanilide-4-hydroxylase (ACOH) (CYP1A2 marker) are the most frequently assayed enzyme activities. The lowest single oral dose of 2,3,7,8-TCDD shown to induce AHH activity in rats was 0.002 µg/kg (Kitchens and Woods 1979). Similarly, the induction of EROD was observed in the liver in Wistar rats (Abraham et al. 1988) and C57BL/6 mice (Harris et al. 1990) following subcutaneous and intraperitoneal injection, respectively. In female $B6C3F_1$ mice, administration of a single oral dose of $0.1 µg 2,3,7,8-TCDD/kg significantly increased liver, lung, and skin EROD activities and liver acetanilide-4-hydroxylase activity (CYP1A2 marker) (Diliberto et al. 1995). In the three tissues examined, induction of EROD was dose-dependent. Also in $B6C3F_1$ female mice, repeated oral administration of doses as low as 1.5 ng 2,3,7,8-TCDD/kg day significantly increased liver, lung, and skin EROD activities and liver acetanilide-4-hydroxylase activity (DeVito et al. 1994). In both studies (DeVito et al. 1994; Diliberto et al. 1995), liver, lung, and skin exhibited different sensitivities for enzyme induction. In male C57BL/6J and DBA/2J mice, the ED_{50}

values for induction of hepatic EROD after a single dose of 2,3,7,8-TCDD were 1.1 and 16 µg/kg, respectively (Weber et al. 1995). In an intermediate-duration dietary study in Sprague-Dawley rats, doses as low as 0.014 µg/kg/day induced both EROD and acetanilide-4-hydroxylase (Van Birgelen et al. 1995). Enzyme induction is a reversible process dependent on the dose and the dosing regime (Fan and Rozman 1995; Li and Rozman 1995). In male C57BL/6N mice, Pegram et al. (1995) showed that induction of acetanilide-4-hydroxylase by 2,3,7,8-TCDD was age-dependent, as it was significantly greater in old than in young mice.

In addition to altering the activities of enzymes from the MFO system in the liver, 2,3,7,8-TCDD also alters the activities of some key liver enzymes of the intermediary metabolism. These effects are intimately related with the wasting syndrome as discussed below (see Body Weight Effects). For example, 2,3,7,8-TCDD decreased the activities of hepatic PEPCK and G-6-Pase (key enzymes of gluconeogenesis) in mice and rats (Fan and Rozman 1995; Li and Rozman 1995; Viluksela et al. 1994; Weber et al. 1995) and also reduced the activity of TdO (key enzyme of tryptophan metabolism) in rats (Li and Rozman 1995; Viluksela et al. 1994), but not in mice (Weber et al. 1995).

Vitamin A (retinol) is essential for normal growth and cell differentiation, particularly for epithelial cells. 2,3,7,8-TCDD has been shown to decrease the storage of vitamin A in rodents. Decreased ability to store vitamin A (retinol) was found in rats and guinea pigs; however, partial recovery of the retinol content by week 16 postexposure was reported only in rats. A single oral dose of 2,3,7,8-TCDD caused a 70% reduction in the liver storage of retinol in rats when measured 2 months postexposure (Thunberg et al. 1979). The reduction was dose-related within the dose range studied (0.1–10 µg/kg) (Thunberg et al. 1980). Reduction of hepatic retinol by 2,3,7,8-TCDD was greater (87%) in younger rats with lower initial weights (Thunberg et al. 1984) than in more mature rats (60%) (Thunberg et al. 1979, 1980). In a 13-week dietary study in female Sprague-Dawley rats, dose of $0.014 µg/kg/day produced a dose-dependent reduction in hepatic retinol (Van Birgelen et al. 1995). In addition to reducing hepatic retinol storage, 2,3,7,8-TCDD exposure induced the activity of UDPGT and AHH in the rat, results obtained with other compounds (polychlorinated phenols, methylcholanthrene, phenobarbital) suggest that the effect is not mediated by the Ah receptor (Thunberg et al. 1984). Experiments with Sprague-Dawley rats showed that pretreatment with 2,3,7,8-TCDD influenced not only the storage, but also urinary and fecal excretion of a subsequent dose of radioactively labeled retinyl acetate. Retinol-content was also altered in various tissues; liver, intestine, and epididymis content decreased by 39–53, 19–67, and 18–44%, respectively, while renal content increased 3–30 times (Håkansson et al. 1989b). The 2,3,7,8-TCDD pretreated rats, though not

retinol-deficient, used a subsequently administered dose of retinyl acetate in a manner similar to retinol-deficient animals.

Mild-to-moderate hepatic effects of 2,3,7,8-TCDD exposure were also found after intermediate-duration dermal exposure in mice (Hebert et al. 1990; NTP 1982a), after acute intratracheal instillation in rats (Nessel et al. 1990, 1992), after acute intraperitoneal exposure in rats (DiBartolomeis et al. 1986; Mason and Safe 1986a), hamsters (Olson et al. 1980a), and guinea pigs (Gasiewicz and Neal 1979; Holcomb et al. 1988; Lu et al. 1986), and after acute subcutaneous exposure in mice (Courtney 1976). Some effects (increased plasma albumin, total protein) were considered to be secondary to progressive dehydration of exposed animals with decreased water consumption (Gasiewicz and Neal 1979).

Hepatotoxicity was observed in rats and mice chronically exposed by gavage to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980). Liver effects were also found in rats exposed by diet to HpCDD (Viluksela et al. 1994), 1,2,3,7,8-PeCDD and 1,2,3,4,7,8-HxCDD (Viluksela et al. 1998b), and OCDD for subchronic durations (Birnbaum et al. 1989a; Couture et al. 1988), and to 2,7-DCDD for a chronic duration (NCI/NTP 1979a).

It is clear that the liver is a target for 2,3,7,8-TCDD toxicity in animals. In humans, hepatic alterations have been observed sometimes following exposure to high 2,3,7,8-TCDD levels. In general, the effects are mild and transient, which might explain the negative findings of Calvert et al. (1992).

Renal Effects. The overall evidence from studies of populations exposed to high concentrations of 2,3,7,8-TCDD suggests that the kidney is not a target for 2,3,7,8-TCDD toxicity in humans (Stehr et al. 1986; USAF 1991; Wolfe et al. 1985).

Likewise, the kidney is not a target organ in adult animals. No effects were found in mice exposed acutely (Holsapple et al. 1986a; Weber et al. 1995) and in rats exposed chronically (Kociba et al. 1978a; NTP 1982b) to 2,3,7,8-TCDD by the oral route or in mice exposed by the dermal route (NTP 1982a). Similarly, no changes were found in rodents exposed chronically to 2,7-DCDD (NCI/NTP 1979a) or a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980) by the oral route.

Renal effects which were seen at near-lethal doses and considered secondary to frank toxicity included pale kidneys in minks after acute oral exposure to 2,3,7,8-TCDD (Hochstein et al. 1988), and enlarged

convoluted tubules and Bowman's spaces together with epithelial hyperplasia in rats (Christian et al. 1986) and monkeys (McConnell et al. 1978a) orally exposed for acute durations and in monkeys orally exposed for intermediate durations (Allen et al. 1977). An increased incidence of renal inflammatory changes recorded in mice after chronic oral exposure to 2,3,7,8-TCDD (NTP 1982b) was not a primary effect. Decreased glomerular filtration rate (Anaizi and Cohen 1978; Pegg et al. 1976) and increased tubular filtration rate (Anaizi and Cohen 1978) were reported in rats treated with a single intraperitoneal dose of 2,3,7,8-TCDD. The authors concluded that observed renal effects were probably secondary to the general toxic reaction to 2,3,7,8-TCDD (Pegg et al. 1976). However, renal effects (mainly hydronephrosis) were found in pups of 2,3,7,8-TCDD-exposed pregnant rodents (Abbott et al. 1987a, 1987b; Courtney 1976; Schwetz et al. 1973) indicating special ability of CDDs to induce effects in the developing kidneys.

Endocrine Effects. No biochemical evidence of thyroid dysfunction, as evaluated by serum levels of T4, triiodothyronine, and TSH, were reported in a group of 18 workers examined 17 years after an industrial accident during the manufacture of 2,4,5-T (Jennings et al. 1988). The small sample size, the fact that no measure of exposure was provided, and the long period of time between exposure and examination preclude any conclusion regarding possible effects of 2,3,7,8-TCDD. Zober et al. (1994) found a significant increase in the incidence of thyroid disease (no further details provided) 35 years after the BASF accident. An increased incidence of diabetes and subclinical decreases in thyroid function were found in Vietnam veterans who participated in operation Ranch Hand (USAF 1991).

A strong positive association was found between glucose intolerance or increased risk of diabetes and 2,3,7,8-TCDD serum levels (USAF 1991). The diabetes finding remained significant even after adjusting for body fat. Furthermore, subclinical effects in thyroid function (significant decrease in mean T3 % uptake and increases in mean TSH) were reported for Operation Ranch Hand veterans with high 2,3,7,8-TCDD serum levels (USAF 1991). However, the magnitude of the differences was not considered physiologically significant. Diabetes and glucose intolerance were also found in workers exposed occupationally (Pazderova-Vejlupkova et al. 1981; Sweeney et al. 1992). However, in the Sweeney et al. (1992) study, age and body mass index, both known risk factors for diabetes, appear to have a greater influence on the increase in both the risk of diabetes and elevated fasting serum glucose levels than 2,3,7,8-TCDD level. A follow-up study of Operation Ranch Hand veterans confirmed earlier findings of glucose abnormalities and increased risk of diabetes mellitus in exposed subjects (Henriksen et al. 1997). Furthermore, a follow-up of Seveso residents found a significant increase in deaths from diabetes among women from zone B (Pesatori et al. 1998).

The evidence available from epidemiological studies suggests that exposure to high concentrations of CDDs may induce long-term alterations in glucose metabolism and subtle alterations (of unknown clinical relevance) in thyroid function.

Numerous studies in rodents have reported alterations in thyroid status after exposure to 2,3,7,8-TCDD. End points commonly examined included serum levels of T4, T3, TSH, and activity of hepatic microsomal UDPGT, an enzyme which increases glucuronation of T4 and clearance. The effects on T4 levels are dose-dependent and also appear to be species-dependent. For example, serum T4 was decreased in rats after acute (Bastomsky 1977; Fan and Rozman 1995; Gorski and Rozman 1987; Henry and Gasiewicz 1987; Hermansky et al. 1988; Potter et al. 1986) and intermediate exposure (Li and Rozman 1995; Sewall et al. 1995; Van Birgelen et al. 1995; Viluksela et al. 1994). In contrast, the response of serum T3 levels ranged from increased (Bastomsky 1977; Potter et al. 1986) to no change or inconsistent change (Fan and Rozman 1995; Henry and Gasiewicz 1987; Potter et al. 1983; Sewall et al. 1995) to decreased (Pazdernik and Rozman 1985). In hamsters, a species less susceptible to 2,3,7,8-TCDD toxicity than rats, T4 serum levels were increased by 2,3,7,8-TCDD even though hepatic microsomal UDPGT activity was significantly increased, suggesting that mechanisms other than induction of this enzyme must account for the species-specific alterations in T4 (Henry and Gasiewicz 1987). A further species-specific response was noted by Weber et al. (1995) who reported that in C57BL/6J and DBA/2J mice, both T4 and T3 levels were decreased in a parallel fashion as a result of a single dose of 2,3,7,8-TCDD. According to Weber et al. (1995), the decrease in T3 in mice would reduce the *de novo* synthesis of fatty acids, thus improving the balance of metabolic energy which might explain, at least in part, the reduced susceptibility of mice to 2,3,7,8-TCDD toxicity compared to rats. It is interesting to note that Long Evans rats exhibited a dose-related increase in T4 and T3 90 days after single doses of 2,3,7,8-TCDD that decreased T4, but did not significantly alter T3 4 days after dosing (Fan and Rozman 1995). The significance of this finding was not entirely clear, but according to the authors it indicated that sustained effects of 2,3,7,8-TCDD on thyroid homeostasis trigger adaptive responses which persist even after most of the 2,3,7,8-TCDD has been cleared. Decreased levels of serum T4 have also been reported in rats administered other CDD congeners such as 1,2,3,7,8-PeCDD and 1,2,3,4,7,8-HxCDD in intermediate exposure duration studies (Viluksela et al. 1998b).

The reduction in circulating T4 levels observed in rats appears, in part, to be due to the increased activity of UDPGT (Bastomsky 1977; Sewall et al. 1995), but other possibilities have also been discussed. McKinney et al. (1985b) proposed that T4 and T3 might be endogenous ligands for the Ah receptor, and

that 2,3,7,8-TCDD might be an agonist for the T4 receptor. Although some evidence was presented in support for this hypothesis, the weight of evidence, summarized by Goldstein and Safe (1989), argues against 2,3,7,8-TCDD being a thyroid agonist. Lans et al. (1993, 1994) have explored the possibility that hydroxylated 2,3,7,8-TCDD metabolites competitively interact with plasma thyroid hormone transport proteins, thus facilitating clearance and excretion of T4. They tested various hydroxy-CDDs in an *in vitro* competitive-binding assay using purified human TTR and found that those with chlorine substitution adjacent to the hydroxy group (7-OH-2,3,8-TrCDD and 2-OH-1,3,7,8-TCDD) showed similar or higher relative-binding potency than T4 (Lans et al. 1993). 8-OH-2,3-DCCD, which did not contain chlorine substitution adjacent to the OH group, did not displace T4. In a subsequent study, Lans et al. (1994) studied the displacement of T4 from globulin, the major T4-binding protein in humans by hydroxy CDD metabolites (in contrast to TTR in rodents). The results showed than none of the tested hydroxylated CDD metabolites inhibited binding of T4 by T4-binding globulin and suggested that hydroxylated CDD metabolites can cause different effects in rodents and humans.

The overall evidence suggests that in rodents, thyroid hormones modify 2,3,7,8-TCDD toxicity, but a reduction in T4 (at least in rats) does not mediate toxicity.

Administration of 2,3,7,8-TCDD to rodents was also shown to reduce blood corticosterone levels (Balk and Piper 1984; DiBartolomeis et al. 1987; Mebus and Piper 1986). This effect has been attributed to decreased corticosterone synthesis by decreasing cholesterol side-chain cleavage in the adrenal gland. More recent studies suggested that 2,3,7,8-TCDD may interfere with secretion or synthesis of appropriate, bioactive ACTH from the anterior pituitary gland, which could compromise adrenal steroidogenenesis (Bestervelt et al. 1993).

Administration of 2,3,7,8-TCDD to animals results in a wide range of endocrine responses which are not only species-dependent, but also exhibit variability within species. Endocrine effects observed in humans have not been limited to thyroid effects and diabetes; alterations in levels of reproductive hormones, as summarized in the sections on reproductive effects have also been observed. The wide array of endocrine effects induced by CDDs and structurally-related chemicals has triggered increased interest within the scientific community and the term “endocrine disruptors” is currently being used to describe some members of this class of chemicals. The available information suggests that CDDs may cause adverse endocrine effects in humans.

Dermal Effects. Chloracne is the most easily recognized effect of exposure to 2,3,7,8-TCDD and structurally related chlorinated organic chemicals. Chloracne is a high-dose response in animals and humans; and its presence in humans indicates exposure to CDDs and other chlorinated organic compounds, but its absence does not preclude such exposure. Furthermore, the variability of the response in more highly exposed individuals suggests that susceptibility varies among individuals. Chloracne can first occur on the face, particularly under the eyes and behind the ears. With increasing exposure, the rest of the face and neck, upper arms, chest, back, abdomen, outer thighs, and genitalia may be affected. When severe, chloracne can cover the entire body. Clinically, changes vary from an eruption of comedones to occurrence of papules and pustules. Histologically, the lesions consist of keratinous cysts caused by squamous metaplasia of sebaceous glands. The acute stage is followed by vermiculite skin atrophy. The incidence of other dermal effects, including hyperpigmentation and hirsutism, correlates with the intensity of chloracne (Poland et al. 1971). Chloracne has been reported to have occurred in at least a small number of workers in all accidents at TCP-production facilities (Jansing and Korff 1994; May 1973; Schecter et al. 1993; Suskind 1985; Zober et al. 1990); among subjects involved in production of 2,3,7,8-TCDD-contaminated products (Bond et al. 1989a; Moses and Prioleau 1985; Pazderova-Vejlupkova et al. 1981; Poland et al. 1971; Suskind and Hertzberg 1984); in laboratory workers exposed to 2,3,7,8-TCDD (Oliver 1975); and among a small percentage of Seveso residents (Assennato et al. 1989; Caramaschi et al. 1981; Mocarelli et al. 1986; Reggiani 1980). Chloracne, however, was not observed among Missouri residents (Hoffman et al. 1986; Webb et al. 1989) examined 10 years after exposure or among Ranch Hand veterans (Burton et al. 1998; USAF 1991).

The dermal changes induced by 2,3,7,8-TCDD may appear as soon as 2 days after exposure (Ott et al. 1993; Zober et al. 1990) or within months (Caramaschi et al. 1981; Reggiani 1980). The lesions may heal within a few months after cessation of exposure (Assennato et al. 1989) despite high serum 2,3,7,8-TCDD levels (Mocarelli et al. 1991) or persist for over 15 years, depending upon severity (Crow 1978; Jansing and Korff 1994; Moses and Prioleau 1985; Schecter et al. 1993; Suskind and Hetzberg 1984). Children exposed to 2,3,7,8-TCDD appear to be more sensitive than adults, and individuals similarly exposed have variable susceptibility to chloracne (Mocarelli et al. 1991). Data from analyses of cases among chemical workers suggested that the risk for developing chloracne was highest among workers who were exposed at younger ages, among those who had been exposed for the longest periods, and among workers whose jobs rated at the highest intensity of exposure (Ott et al. 1987). The variability in the chloracneic response can be illustrated the following evidence from the Seveso incident: no chloracne was observed in subjects with initial serum lipid 2,3,7,8-TCDD levels of <800 ppt, chloracne was present at serum lipid levels of

>12,000 ppt; and between 800 and 12,000 ppt the occurrence of chloracne was sporadic (Mocarelli et al. 1991); this suggested that, in this population, 8,000 to 10,000 ppt 2,3,7,8-TCDD in blood was necessary for expression of chloracne. German workers involved in TCP production who had chloracne had estimated adipose levels $200 ppt 2,3,7,8-TCDD and $2,000 ppt HxCDD at the time of diagnosis (Beck et al. 1989a). In another study of German workers, 80% of the severe chloracne cases had 2,3,7,8-TCDD levels of $250 ppt; however, 26% of the workers without chloracne also had 2,3,7,8-TCDD levels of $250 ppt (Ott et al. 1993). Schecter et al. (1993) provided the first reported incidence of chloracne in females with elevated dioxin blood levels from occupational exposure. Their observation that one worker diagnosed with chloracne in their study had the lowest 2,3,7,8-TCDD blood concentration, whereas two workers with the higher levels did not display chloracne, confirmed the view that chloracne indicates exposure to dioxin, but its absence does not preclude such exposure.

No studies were located regarding dermal effects in humans exposed specifically to CDDs by the oral route. Evidence from human case reports in the Yusho/Yu-Cheng incidents (which involved exposure to CDFs, PCBs, and CDDs) and from animal studies, however, indicates that dermal effects could occur after exposure by the oral route (ATSDR 1994).

Oral studies of 2,3,7,8-TCDD showed the development of rough hair in hamsters (Henck et al. 1981) and skin thickening in A2G-hr/+ mice (Greig 1984) after acute exposure. Chronic oral exposure to 2,3,7,8-TCDD caused dermatitis in B6C3F_1 mice (Della Porta et al. 1987) and amyloidosis in Swiss mice (Toth et al. 1979). Rhesus monkeys proved to be very sensitive to 2,3,7,8-TCDD-induced dermal effects. The changes consisted of swollen eyelids, nail loss, facial alopecia, and acneform lesions after both acute- (McConnell et al. 1978a) and intermediate-duration oral exposures (Allen et al. 1977; McNulty 1984). Dermal exposure to 2,3,7,8-TCDD induced hyperkeratosis and epidermal hyperplasia in hairless HRS/J mice after acute- (Puhvel and Sakamoto 1988) and intermediate-duration (Puhvel et al. 1982) exposures. While acneiform lesions were reported in CD-1 mice after intermediate-duration dermal exposure to 2,3,7,8-TCDD (Berry et al. 1978, 1979), no effects were found in Swiss Webster mice chronically exposed to lower levels (NTP 1982a).

The data available suggest that 2,3,7,8-TCDD is a dermal toxicant both in humans and animals. Erythematous skin rashes and chloracne are considered one of the hallmarks of 2,3,7,8-TCDD toxicity, although it can be caused also by exposure to other polyhalogenated aromatic compounds. It is also worth

mentioning that although in humans chloracne indicates exposure to chlorinated or halogenated aromatics, lack of chloracne does not indicate that exposure has not occurred.

Ocular Effects. The incidence of eye irritation correlated with the intensity of chloracne in a study of workers employed in a 2,4,5-T factory (Poland et al. 1971), but the role of 2,3,7,8-TCDD, if any, cannot be established. No studies were located regarding ocular effects in humans exposed specifically to CDDs by the oral route. Evidence from the human case reports in the Yusho/Yu-Cheng incidents (which involved exposure to CDFs, PCBs, and less so CDDs) and from animal studies, however, indicates that ocular effects could occur after exposure by the oral route (ATSDR 1994). Ocular effects observed in the Yusho and Yu-Cheng victims included hypersecretion of the Meibomian glands, abnormal pigmentation of the conjunctiva, and swelling of the eyelids (Hsu et al. 1994; Masuda 1994).

Topical application of 2,7-DCDD, with no toxic 2,3,7,8-chlorine pattern, 2,3,7,8-TCDD, and mixed HxCDD, or OCDD into the conjunctival sac of rabbits caused transient pain and conjunctival inflammation (Schwetz et al. 1973).

Based on adverse ocular effects observed in humans and animals exposed to chemicals structurally-related to CDDs and animals (monkeys) exposed to 2,3,7,8-TCDD itself, it is reasonable to assume that CDDs will cause similar effects under similar exposure conditions.

Body Weight Effects. A transient weight loss was reported in a small number of subjects exposed to 2,3,7,8-TCDD in the workplace (Jirasek et al. 1976; Oliver 1975). However, due to the lack of data from controlled studies, the role of 2,3,7,8-TCDD, if any, is difficult to ascertain. Although weight loss has not been well documented in humans following exposure to 2,3,7,8-TCDD, numerous animal studies provide evidence that exposure to CDDs causes the wasting syndrome. Acute oral exposure to 2,3,7,8-TCDD induced weight loss in rats (Christian et al. 1986a; Moore et al. 1985; Roth et al. 1988; Seefeld and Peterson 1984; Seefeld et al. 1984a, 1984b; Walden and Schiller 1985), mice (Hanberg et al. 1989; Kelling et al. 1985; Smith et al. 1976; Weber et al. 1995), guinea pigs (Hanberg et al. 1989; Umbreit et al. 1985), hamsters (Hanberg et al. 1989), and monkeys (McConnell et al. 1978a). Similarly, body weight changes were found after intermediate-duration oral exposure to 2,3,7,8-TCDD in rats (Diliberto et al. 1996; NTP 1982b; Van Birgelen et al. 1995; Viluksela et al. 1994; Vos et al. 1973), guinea pigs (DeCaprio et al. 1986; Vos et al. 1973), mice (Thigpen et al. 1975; Vos et al. 1973), and monkeys (McNulty 1984), and after chronic exposure in rats (Kociba et al. 1978a; NTP 1982b; Van Miller et al. 1977) and mice (Della

Porta et al. 1987). In addition, milder changes, represented usually by decreases in body weight gain, were seen after oral exposure to other congeners (NCI/NTP 1979a, 1980; Schwetz et al. 1973). The wasting syndrome does not appear to be a route-specific effect since body weight changes were observed in mice exposed to 2,3,7,8-TCDD dermally (NTP 1982a; Puhvel et al. 1982), and numerous studies reported body weight changes in animals that were injected with 2,3,7,8-TCDD subcutaneously or intraperitoneally (Canga et al. 1988; Chahoud et al. 1989; Della Porta et al. 1987; Gorski et al. 1988b; Holcomb et al. 1988; Kelling et al. 1985; Lu et al. 1986; McConkey and Orrenius 1989; Pohjanvirta et al. 1989).

The mechanism of the wasting syndrome has been extensively investigated. Results of studies in C57BL/6 mice, guinea pigs, and Fischer 344 rats showed that 2,3,7,8-TCDD exposure induces appetite suppression resulting in loss of adipose and lean tissue, and eventually death (Kelling et al. 1985). However, by using pair-fed animals as controls, it was clear that body weight loss alone was not the cause of death. This is also supported by the fact that the weight loss, but not the lethality of 2,3,7,8-TCDD, can be prevented by parenteral feeding of rats and guinea pigs (Gasiewicz et al. 1980; Lu et al. 1986). Seefeld and Peterson (1984) showed that in rats, fecal energy loss as a percentage of daily feed energy uptake was not significantly altered by treatment with 2,3,7,8-TCDD. Furthermore, the percentage of feed energy absorbed by the gastrointestinal tract was not changed by 2,3,7,8-TCDD, which ruled out the possibility of a 2,3,7,8-TCDD-induced gross malabsorption syndrome. The same group of investigators (Seefeld et al. 1984a, 1984b) showed that 2,3,7,8-TCDD does not impair the animals' capacity to feed since rats that lost weight prior to treatment with 2,3,7,8-TCDD ate and gained weight after treatment with 2,3,7,8-TCDD. Based on their results, Seefeld and coworkers (Seefeld and Peterson 1984; Seefeld et al. 1984a, 1984b) proposed that 2,3,7,8-TCDD lowers a “set point” for regulated body weight, and hypophagia serves as a secondary response to reduce the animal’s body weight to the lower regulation level determined by the dose of 2,3,7,8-TCDD administered. The ability of an animal to recover from the 2,3,7,8-TCDD-induced hypophagia may be species- and/or strain-specific (Tuomisto and Pohjanvirta 1991). Within 1-2 weeks after a single dose of 2,3,7,8-TCDD, feed intake increased in Hans/Wistar rats but not in Long Evans rats; the Long Evans rats died by week 3. Although Hans/Wistar and Long Evans rats have similar Ah receptor binding and cytochrome P-450 induction properties, the wide differences in sensitivity to 2,3,7,8-TCDD suggest that other mechanisms may be involved in the wasting syndrome.

Numerous studies have examined the possibility that the wasting syndrome results from 2,3,7,8-TCDD-induced alterations in intermediate metabolism. For example, it has been shown that in male Sprague-Dawley rats, lethal doses of 2,3,7,8-TCDD severely alter glucose homeostasis (Gorski and Rozman 1987;

Gorski et al. 1990; Potter et al. 1983). Hypoglycemia was not the result of hyperinsulinemia since insulin levels were also depressed with 2,3,7,8-TCDD treatment (Potter et al. 1983). Also, hypophagia did not account for hypoglycemia since pair-fed rats also exhibited hypoglycemia (Potter et al. 1983). Further studies showed that decreased gluconeogenesis was the result of significantly reduced activity of hepatic PEPCK, the rate-determining enzyme in the pathway (Weber et al. 1991a). Other gluconeogenic enzymes such as glucose-6-phosphatase and pyruvate carboxylase were also decreased by treatment with 2,3,7,8-TCDD, but pyruvate kinase, a glycolytic enzyme, was not affected (Weber et al. 1991a). It was also shown that changes in gluconeogenic enzyme activities preceded hormonal changes (insulin, corticosterone) by at least 2 days (Weber et al. 1991b), which led the authors to suggest that 2,3,7,8-TCDD-induced changes in hormonal homeostasis are adaptive responses of the organism to stimulate gluconeogenesis. Reduced liver PEPCK activity as a result of 2,3,7,8-TCDD treatment has also been observed in Long Evans rats (Fan and Rozman 1995) and in C57BL/6J and DBA/2J mice (Weber et al. 1995).

Some investigators suggested that the wasting syndrome may be linked to 2,3,7,8-TCDD-induced effects on the thyroid (Rozman 1984; Rozman et al. 1985). In thyroidectomized rats, the weight loss after 2,3,7,8-TCDD exposure was slow, suggesting that the lack of thyroid hormone reduced the rate of stored fat utilization (Rozman et al. 1985). Thyroidectomy protected rats from immunotoxicity induced by an intraperitoneal dose of 2,3,7,8-TCDD (Pazdernik and Rozman 1985). Replacement therapy with T4 partially reversed the effects of thyroidectomy on T4 and triiodothyronine serum levels, body weight, and immune function. The authors suggested that 2,3,7,8-TCDD-induced hypothyroidism may be a protective mechanism against 2,3,7,8-TCDD-induced wasting syndrome and lethality. Thyroid hormones regulate fat mobilization and use of fatty acids in adipose tissue and influence norepinephrine-mediated nonshivering thermogenesis that is also linked to brown adipose tissue. It was also suggested that the effect of 2,3,7,8-TCDD on the thyroid causes activation of thyrotropin-releasing hormone, which results in anorexia (Aust 1984). Anorexia and 2,3,7,8-TCDD-induced retinol depletion would then lead to the body weight loss.

Based on the findings that 2,3,7,8-TCDD administered into the lateral cerebral ventricles does not cause death or decreased feed intake in rats (Stahl and Rozman 1990), Rozman et al. (1991) examined the possibility that 2,3,7,8-TCDD suppresses appetite via peripheral mechanisms acting on the central nervous system. The results of experiments of transfusion of blood from rats with 2,3,7,8-TCDD-induced appetite suppression and normal satiated rats suggested that 2,3,7,8-TCDD-treated rats are not satiated, rather than

that they are not hungry. In a second experimental series, the possible role of norepinephrine, dopamine, and serotonin as central mediators of appetite suppression induced by 2,3,7,8-TCDD was investigated. No changes were found in epinephrine and dopamine in the hypothalamus or in dopamine and its metabolites in the striatum. However, tryptophan (a precursor of serotonin) levels in plasma and brain were increased and this was paralleled by increases in brain serotonin and 5-hydroxyindolacetic acid (the major serotonin metabolite) (Rozman et al. 1991). Based on the results of these experiments, Rozman et al. (1991) proposed that decreased PEPCK activity decreases gluconeogenesis and leads to increased plasma concentrations of glycogenic amino acids, such as tryptophan. Increased tryptophan leads to increase in serotonin release in the brain and to appetite suppression. It was subsequently shown, however, that lethal doses of 2,3,7,8-TCDD reduces the activity of TdO, the key enzyme of the major tryptophan degradation pathway (Weber et al. 1992c, 1994). Whether due to reduction in TdO activity, reduced glyconeogenesis, or both, Weber et al. (1994) proposed that an initial increase in tryptophan levels result in some initial feed refusal, which in turn initiates the wasting of body mass and increases the supply of tryptophan with which the animals cannot deal. A vicious cycle develops which results in strongly elevated tryptophan levels and increased serotonin turnover, which acts as an appetite suppressant.

Alternative explanations for the increased levels of plasma-free tryptophan in 2,3,7,8-TCDD-treated rats have been offered. Four possibilities were discussed by Unkila et al. (1994): 2,3,7,8-TCDD may reduce the binding capacity of the blood, i.e., may decrease plasma albumin levels; 2,3,7,8-TCDD may stimulate the production of some competing factor in the blood (e.g., nonesterified fatty acids or bilirubin) which are also bound to albumin; 2,3,7,8-TCDD might affect the binding properties of the albumin molecule; and 2,3,7,8-TCDD might inhibit tryptophan catabolism. Of the four factors examined that might affect the binding of tryptophan to albumin, Unkila et al. (1994) indicated that the most important is probably plasma bilirubins and suggested that disturbances in liver function may be involved in the changes in tryptophan metabolism.

The wasting syndrome is a characteristic effect of exposure to 2,3,7,8-TCDD in animals and, in its most severe form, is usually associated with lethality, particularly in rodents. The fact that the wasting syndrome has not been demonstrated in humans does not necessarily indicate that humans are insensitive to this effect of dioxins, but may indicate that human exposure has not approached acutely high enough levels.

Immunological and Lymphoreticular Effects. No consistent exposure-related effects on the immune system have been observed in human populations exposed to above-background levels of 2,3,7,8-TCDD (Ernst et al. 1998; Jansing and Korff 1994; Jennings et al. 1988; Jung et al. 1998; Mocarelli et al. 1986; Neubert et al. 1993, 1995; Svensson et al. 1994; Tonn et al. 1996; USAF 1991; Webb et al. 1989; Zober et al. 1994). The immunological effects of 2,3,7,8-TCDD were recently reviewed by Kerkvliet (1995) who identified a number of factors on which the results of immunological assessments may be dependent. One of these factors, perhaps the most notable, is the inherent difficulty in assessing subclinical immunological effects in an outbred human population. In addition, the wide range of normal responses of most immunological assays diminishes the sensitivity to detect small changes. Another factor to consider is that assays used to assess immune function in humans exposed to 2,3,7,8-TCDD and related chemicals have been based for the most part on what was clinically feasible rather than on assays proven to be sensitive in animal studies (i.e., the antibody response to SRBC). Therefore, the lack of consistent or significant immunotoxic effects in humans exposed to 2,3,7,8-TCDD may be a function of both the type of assay and the immune status of the population studied. Furthermore, often the cohort exposure is not validated and the immune status has been examined long after exposure allowing for recovery from any immunotoxic effect that may have occurred shortly after exposure.

A potentially useful approach to studying the sensitivity of the human immune system to 2,3,7,8-TCDD has been to examine the direct *in vitro* effects of 2,3,7,8-TCDD on human cell cultures. For example, Cook et al. (1987a) observed concentration dependent immunosuppressive responses of cultured human thymic epithelial cell and thymocytes exposed to 2,3,7,8-TCDD. The proliferative response of human lymphocytes *in vitro* to stimulation with mitogens is extremely sensitive to 2,3,7,8-TCDD. Concentrations of 2,3,7,8-TCDD as low as 10^{-12} to 10^{-14} M reduced the percentage of $CD20^+$ B cells and $CD4^+CDw29^+$ T cells (Neubert et al. 1991). However, these results could not be corroborated in a similar study by Lang et al. (1994) who used 2,3,7,8-TCDD concentrations ranging from 10^{-7} to 10^{-11} M. In another study, proliferation of human tonsillar lymphocytes (HTLs) cultured *in vitro* was inhibited by 3×10^{-8} M 2,3,7,8-TCDD, but pokeweed mitogen (PWM) induced proliferation was not affected by 2,3,7,8-TCDD concentrations ranging from 3×10^{-8} to 10^{-10} M (Wood et al. 1992). However, when low density ß cells from HTLs were purified and cultured *in vitro* in the same laboratory and stimulated with lipopolysaccharide and TRF (T-cell replacing factor), 3×10^{-8} to 10^{-10} M 2,3,7,8-TCDD suppressed the IgG secretion in a dose related manner. HTLs possess the Ah receptor as indicated by the induction of 7-ethoxycoumarin-o-deethylase (EROD) in a dose-related manner at the above doses when the HTLs are stimulated with phytohemagglutenin (PHA) or PWM (Wood et al. 1993). A promising animal model for

assessing the potential immunotoxicity of CDDs in humans is the SCID mice, which can be engrafted with human fetal thymus and liver tissue fragments under the kidney capsule. Using the SCID mice model, it was shown that human thymus cells are as sensitive to 2,3,7,8-TCDD as the thymus of Wistar rats (De Heer et al. 1995).

The immune system appears to be one of the most sensitive targets for CDDs in animals. However, it is difficult to make interspecies or congener comparisons due to interlaboratory variability of functional tests and use of different end points in various studies. Thymic atrophy was observed in rats, mice, guinea pigs, (De Heer et al. 1994a; Hanberg et al. 1989), hamsters (Hanberg et al. 1989; Olson et al. 1980a), and monkeys (McConnell et al. 1978a) after acute exposure; in guinea pigs (Vos et al. 1973) after intermediate-duration exposure; and in rats (Kociba et al. 1978a) after chronic oral exposure to 2,3,7,8-TCDD. Furthermore, lymph node atrophy (Allen et al. 1977) and bone marrow degeneration (Hong et al. 1989) were reported in monkeys after intermediate- and chronic-duration exposure to 2,3,7,8-TCDD, respectively. In support of these data, thymic atrophy was also induced by a single intraperitoneal injection of 2,3,7,8-TCDD in Sprague-Dawley rats (Gorski et al. 1988b), Syrian hamsters (Olson et al. 1980a), and C57BL/6J mice (Poland and Glover 1980). Only increased thymus/body weight ratio was found in HRS/J mice exposed to 2,3,7,8-TCDD dermally (Hebert et al. 1990). Effects on peripheral lymphocytes following acute subcutaneous and *in vitro* exposure, particularly changes in percentages of lymphocyte subpopulations, suggest that marmoset monkeys may be particularly sensitive to immunologic effects of 2,3,7,8-TCDD (Neubert et al. 1990a, 1991). In general, relatively high doses cause lymphoid depletion, lower doses cause thymic cellular depletion in young animals, and much lower doses affect specific immune receptor functions.

Administration of total parenteral nutrition did not protect rats from thymic atrophy with decreased numbers of cortical lymphocytes that developed after acute intraperitoneal 2,3,7,8-TCDD exposure (Gasiewicz et al. 1980). 2,3,7,8-TCDD-induced thymic atrophy in BALB/CJ and DBA/2J mice correlated with a reduction in thymic and bone marrow terminal deoxynucleotidyl transferase synthesis (Fine et al. 1990b). The prothymocyte activity was severely damaged by 2,3,7,8-TCDD exposure. The authors concluded that 2,3,7,8-TCDD produces atrophy by damaging the capability of bone marrow prethymic stem cells to seed the thymus. In addition to bone marrow effects, 2,3,7,8-TCDD may also inhibit normal thymocyte maturational processes. When $B6C3F_1$ mice were exposed *in utero* by dosing the dam at 3 µg/kg/day between Gd 6–14 and foster-nursing the offspring with unexposed females, thymic atrophy was seen at Gd 18 or on postnatal day 6, but the thymic effects were no longer seen by day 14. *In utero*

effects on the thymus were at much lower doses than effects in animals exposed postnatally. Rodents are born with an immature immune system which develops in the first few days after birth. These mice were tested for immune function at 7–8 weeks of age; the cytotoxic T-lymphocyte was still suppressed, but the mitogen response to SRBC was not suppressed (Holladay et al. 1991). Humans, in contrast to rodents, have a more mature immune system at birth. The role of the thymus is important in prenatal and perinatal development of the immune system, but its role in adult life has not been established. Concentrations of 140 fg 2,3,7,8-TCDD/mg in the thymus of mice at Gd 18 were associated with thymic atrophy (Fine et al. 1990a).

In addition to causing lymphoid organ weight changes, 2,3,7,8-TCDD has been shown to cause functional alterations in the immune response (Vecchi et al. 1980a). Studies have shown that suppressed antibody response (Holsapple et al. 1986a; Vecchi et al. 1980a, 1983b) decreased host resistance to *Streptococcus pneumoniae* or influenza A virus (Burleson et al. 1996; White et al. 1986), and suppressed serum complement activity (White et al. 1986) occur in $B6C3F_1$ mice after single or repeated oral dose(s) of 2,3,7,8-TCDD. Immunological effects occurred at the lowest LOAEL in acute- and intermediate-duration exposure studies and indicated that the immunological system is very sensitive to 2,3,7,8-TCDD-induced toxicity. The dose of 0.01 µg/kg for impaired resistance was the lowest LOAEL for acute oral exposure (Burleson et al. 1996). The NOAEL of 0.005 µg/kg identified in this study was used to derive an acute oral MRL of 2×10^{-4} µg/kg/day. The 0.0007 µg/kg/day dose for reduced thymus weight for intermediate-duration oral exposure (DeCaprio et al. 1986) was used to derive an intermediate-duration oral MRL for 2,3,7,8-TCDD of 2×10^{-5} µg/kg/day. Immunosuppression as evidenced by increased mortality when challenged with bacteria was demonstrated in C57BL/6J mice after administration of a dose of 1 µg 2,3,7,8-TCDD/kg/week over a period of 4 weeks (Thigpen et al. 1975); this occurred without any other apparent signs of toxicity. In addition, an intermediate-duration exposure to 2,3,7,8-TCDD induced decreased cell-mediated (mice and guinea pigs) and humoral (guinea pigs) immunity (Vos et al. 1973). The results indicated that guinea pigs are the most sensitive species tested. 2,3,7,8-TCDD-induced suppression of humoral immunity was also reported in animals exposed parenterally.

In general, the route of exposure does not affect the immune response. Several tests of immunotoxicity dosed the animals by parenteral routes (intravenous, subcutaneous, or intraperitoneal). Acute intraperitoneal 2,3,7,8-TCDD exposure inhibited the primary and secondary humoral response to T-dependent (SRBC) and T-independent (pneumococcal polysaccharide) antigens in C57BL/6 mice (Vecchi et al. 1980b, 1983b); doses were comparable to those causing effects by the oral route. A dose-

related suppression of IgM and IgG antibody-forming cells was induced by exposure to a single intraperitoneal injection of 2,3,7,8-TCDD in $B6C3F_1$ mice (House et al. 1990). Furthermore, doses as low as 0.1 µg/kg decreased survival after influenza virus infection, and exposure at 10 µg/kg suppressed production of antibody to viral hemagglutinin. Cytolytic and NK-cell-mediated immunity was impaired in C57BL/6 mice after a single intraperitoneal injection of 2,3,7,8-TCDD due to the decreased number of peritoneal macrophages and splenocytes (Mantovani et al. 1980). However, the immune function per unit was not damaged. In addition, an *in vitro* study demonstrated that 2,3,7,8-TCDD induces tumor necrosis factor in human keratinocytes that could affect tumor promotion and affect immune parameters (Choi et al. 1991).

The role of the Ah receptor in the immune responses to CDDs has been examined in several studies. A correlation between the AHH inducibility and suppression of humoral immunity caused by 2,3,7,8-TCDD injection was observed in several strains of mice (Vecchi et al. 1983a). Similarly, when three strains of Ah responsive mice (C57BL/6nQdj, BALB/cCrj, C3H/HeNQdj) were compared with nonresponsive (AKR/JSea, DBA/2JCrj, DDD:Qdj) strains of mice, decreased thymus weight was found only in the responsive animals (Nagayama et al. 1989). The C57 strain also had decreased lymphocyte counts. Results of an *in vitro* experiment supported these observations (Dencker et al. 1985). Thymus cultures from Ah locus responsive C57BL/6 mice were very sensitive to the toxicity of 2,3,7,8-TCDD compared with thymus cultures from the nonresponsive DBA/2J mice. 2,3,7,8-TCDD exposure of cultures of thymic epithelial cells from responsive C57BL/6 mice indicated that 2,3,7,8-TCDD alters the maturation of thymocytes (Greenlee et al. 1985). It was further demonstrated that 2,3,7,8-TCDD toxicity in human thymic epithelial cells was mediated by a protein receptor (Cook and Greenlee 1989). Similarly, *in vitro* studies with lymphocytes, spleen cells, and bone marrow cells from 2,3,7,8-TCDD-pretreated mice indicated that 2,3,7,8-TCDD acts by an Ah locus-dependent mechanism to obstruct the formation of cytotoxic T cell generation from their precursors (Dooley et al. 1990; Holladay et al. 1991; Nagarkatti et al. 1984). A brief summary of the possible mechanisms of 2,3,7,8-TCDD immunotoxicity can be found in Section 2.4.2.

Oral experiments with other congeners reported suppressed antibody response in $B6C3F_1$ mice after acute exposure to 2,7-DCDD, a non 2,3,7,8-chlorine substituted CDD (Holsapple et al. 1986b) and splenic hyperplasia in rats after intermediate-duration exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980).

Although human exposure studies to date found no conclusive evidence of immunotoxicity, the animal data show that the immune system is a target for CDD toxicity in many species. However, a defined 2,3,7,8-TCDD-induced immune deficiency syndrome has not emerged largely because in animals, the immune response depends on the species studied, the dose of 2,3,7,8-TCDD, and the antigen and exposure protocol studied.

Neurological Effects. Some psychological effects were reported in Vietnam veterans potentially exposed to 2,3,7,8-TCDD-contaminated herbicides. These included depression in Air Force and ground troop veterans (Levy 1988; Wolfe et al. 1985) and hypochondria and hysteria in Air Force veterans (Wolfe et al. 1985). In contrast, a more recent study did not find any association between 2,3,7,8-TCDD exposure and neurological or psychological diseases in Air Force personnel (USAF 1991). These psychological effects could be due to a number of stress-related factors in the veterans. Recently, a group of 16 scientific experts from the National Academy of Sciences' Institute of Medicine, who evaluated the strength of evidence for human health effects among veterans exposed to herbicides used in Vietnam, found no strong evidence establishing an association between herbicide use in Vietnam and clinical neurologic disorders (Goetz et al. 1994). However, psychological changes were reported in relatively small cohorts of exposed individuals (Oliver 1975; Pazderova-Vejlupkova et al. 1981; Peper et al. 1993). Subclinical peripheral neuropathy, encephalopathy, and sensory impairment were reported in workers exposed to higher levels of 2,3,7,8-TCDD (Goldman 1973; Jirasek et al. 1976; Pazderova-Vejlupkova et al. 1981) and in the general population exposed to 2,3,7,8-TCDD after an industrial accident (Barbieri et al. 1988; Filippini et al. 1981; Pocchiari et al. 1979). Decreased nerve conduction velocity was observed in phenoxy herbicide production workers (Singer et al. 1982). In contrast, exposure to 2,3,7,8-TCDD (confirmed by elevated serum levels) was not related to chronic peripheral neuropathy in a group of workers exposed 15–37 years earlier compared to referent controls (Sweeney et al. 1993). These authors suggest that the finding of peripheral neuropathy in the earlier studies indicate that this condition may occur shortly after exposure and resolve over time.

Data regarding neurological or neurophysiological effects following exposure to CDDs in animals are limited. Decreased motor activity was seen in rats at 2,3,7,8-TCDD dose levels of #5 µg/kg (Giavini et al. 1983; Seefeld et al. 1984a). Time-dependent increases in tryptophan (amino acid precursor of the neurotransmitter serotonin) levels in plasma and brain (hypothalamus, striatum) correlated with elevations in brain serotonin and 5-hydroxyindoleacetic acid levels in rats after a single intraperitoneal injection of 50 or 120 µg 2,3,7,8-TCDD/kg (Rozman et al. 1991; Tuomisto et al. 1990). Furthermore, slight changes

were observed in levels of noradrenaline, dopamine, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) (Tuomisto et al. 1990). Results from a more recent study in rats showed that 2,3,7,8-TCDD increases neuronal serotonin turnover in TCDD-susceptible Long Evans rats, but not in TCDD-resistant Han/Wistar rats or in food-restricted Long Evans rats (Unkila et al. 1994). By using much lower intraperitoneal doses of 2,3,7,8-TCDD (2.2–8.8 μg/kg) in adult male Han/Wistar rats, thus avoiding manifestation of the wasting syndrome, Grahmann et al. (1993) and Grehl et al. (1993) observed electrophysiological (decreased conduction velocity) and histological signs (nerve degeneration) of peripheral neuropathy several months after a single injection of 2,3,7,8-TCDD. The possible mechanism of 2,3,7,8-TCDD neurotoxicity was not discussed. The existing information suggests that 2,3,7,8-TCDD causes minor alterations in brain neurotransmitter systems.

The overall evidence suggests that adverse neurological effects may occur in subjects exposed to relatively high levels of dioxins, or at least to levels that cause frank dermal effects. The neurological effects, however, may be transient and therefore, difficult to diagnose if examination is conducted several years after exposure. The nervous system in adults does not seem to be a particularly sensitive target for CDDs toxicity, but CDDs may represent a neurological hazard to the developing organism by, for example, altering hormone levels at critical times during the maturation of the central nervous system.

Reproductive Effects. The weaknesses of the epidemiology studies examining reproductive end points limits drawing conclusions regarding the reproductive toxicity of 2,3,7,8-TCDD in humans. Some common weaknesses include lack of exposure data (many of the studies rely on self-reported 2,3,7,8-TCDD exposure; CDC (1987) found that 2,3,7,8-TCDD blood levels of Vietnam veterans reporting direct or indirect exposure to Agent Orange were not significantly different from levels in non-Vietnam veterans), concomitant exposure to other chemicals, and lack of data on 2,3,7,8-TCDD levels at the time of conception. Several studies looked for an association between 2,3,7,8-TCDD exposure and an increased risk of spontaneous abortions, most did not find any statistically significant alterations following paternal exposure to 2,3,7,8-TCDD (Aschengrau and Monson 1989; Smith et al. 1982; Wolfe et al. 1995). An increased incidence of spontaneous abortions, was observed in women living near an herbicide manufacturing facility (Forsberg and Nordstrom 1985). However, this study has been criticized for its small sample size, inadequate discussion of sample selection, and concomitant exposure to other chemicals, including dibenzofurans (Sweeney 1994). In Vietnamese residents living in areas sprayed with Agent Orange, an increased incidence of hydatiform moles was observed (Phuong et al. 1989a). A later case-

control study by Ha et al. (1996) did not confirm the results of the Phuong et al. (1989a) study. In the 7½-year period after the Seveso accident, the number of female children born to parents living in area A was significantly higher than the number of male children (48 versus 26) (Mocarelli et al. 1996). An increased ratio of female to male children was also reported in workers of a 2,4,5-T production facility in Ufa, Russia (Basharova 1996) and in men exposed to chlorophenate wood preservatives contaminated with CDD (Dimich-Ward et al. 1996; James 1997). No alterations were found in the Missouri cohort of women living in 2,3,7,8-TCDD-contaminated areas (Stockbauer et al. 1988). Although several studies provide suggestive evidence of a relationship between CDD exposure and alterations in the sex ratio, the data are inadequate to establish a causal relationship. Additionally, it is not known how 2,3,7,8-TCDD affects the sex ratio. It has been postulated that the effect may be due to an alteration in hormonal balance or a disproportional number of miscarriages of male fetuses.

Data on 2,3,7,8-TCDD-induced alterations in gonads and reproductive endocrine function in humans are limited to effects observed in males. Decreased testicular size without any hormonal changes was found in Air Force Vietnam veterans exposed to 2,3,7,8-TCDD during Operation Ranch Hand (USAF 1991). This finding (decreased testicular size) was not confirmed when a more sensitive measurement device (ultra-sound) was used (Henriksen et al. 1996). Wolfe et al. (1985) found no alterations in sperm count or morphology in veterans involved in Operation Ranch Hand. Henriksen et al. (1996) assessed the possible relationship between 2,3,7,8-TCDD exposure and alterations in testosterone levels, FSH, LH, testicular abnormalities, sperm abnormalities, and sperm counts in the Operation Ranch Hand cohort (reproductive parameters were assessed in 1982, 1987, and 1992) and found no consistent, statistically significant alterations. Increases in FSH and LH levels and decreases in testosterone levels were observed in males working in 2,4,5-trichlorophenol manufacturing facilities (NIOSH cohort); however the magnitude of the changes in hormone levels was small (Egeland et al. 1994). The study authors note that increases in LH levels and decreases in testosterone levels were not found in the same men, suggesting that 2,3,7,8-TCDD may result in subtle alterations rather than primary gonadal failure.

A number of reproductive effects, including decreased fertility, damage to the gonads, and alterations in hormone levels, have been observed in male and female animals orally exposed to 2,3,7,8-TCDD. In male rats, a dose- and time-dependent reduction of serum testosterone and dihydrotestosterone levels was observed after acute oral exposure to 2,3,7,8-TCDD (Mebus et al. 1987; Moore et al. 1985, 1991). Furthermore, male rats had decreased weight of seminal vesicles following oral exposure to 2,3,7,8-TCDD (Al-Bayati et al. 1988; Moore et al. 1985) and reduced spermatogenesis after oral and subcutaneous

exposure (Al-Bayati et al. 1988; Chahoud et al. 1989; Van Miller et al. 1977). Biochemical changes in rat testes included dose- and time-dependent decreases in 17-hydroxylase activity and 20-lyase activity and reduced microsomal cytochrome P-450 (Mebus et al. 1987). Decreases in testicular superoxidase dismutase and glutathione peroxidase activities, and increases in protein kinase C activity and lipid peroxidation were also found in 2,3,7,8-TCDD-exposed rats (Al-Bayati et al. 1988). On the basis of the above data, it was postulated that the androgen deficiency is due to decreased androgen synthesis. It was further suggested that the morphological changes in rat testes may be due to changes in lipid peroxidation.

Pre- and/or postimplantation losses have been observed in rats (Giavini et al. 1983; Sparschu et al. 1971a), mice (Neubert and Dillman 1972; Smith et al. 1976), and rabbits (Giavini et al. 1982) following acute oral exposure to 2,3,7,8-TCDD. A single intraperitoneal injection of 2,3,7,8-TCDD (100 µg/kg) given between Gd 2–6 caused a high incidence of resorptions in C57BL/6J mice (Pratt et al. 1984). Similarly, increased resorptions were reported in rats exposed to mixed HxCDD during gestation, but not in those exposed to 2,7-DCDD or OCDD (Schwetz et al. 1973). In addition, abortions were observed in monkeys exposed to 2,3,7,8-TCDD for 3 weeks by gavage (McNulty 1984), and reduced reproduction was observed in those exposed chronically in the feed (Bowman et al. 1989b; Hong et al. 1989; Schantz et al. 1992). Finally, significantly decreased fertility in F_1 and F_2 generations was reported in a 3-generation reproductive study in rats exposed to 2,3,7,8-TCDD (Murray et al. 1979).

Investigations into the mechanism of CDD-induced decreased fertility revealed blocked estrous cycle in female mice exposed orally to 2,3,7,8-TCDD for an intermediate duration (Umbreit et al. 1987) and dose-dependent decreases in uterine and hepatic cytosolic, and nuclear estrogen and progesterone receptor levels in rats after intraperitoneal 2,3,7,8-TCDD injection (Romkes and Safe 1988). Furthermore, 2,3,7,8-TCDD antagonized the estradiol-mediated increases in these levels. In addition, a dose-related reduction of uterine peroxidase activity and decreased uterine wet weight were seen after a single 2,3,7,8-TCDD injection in rats (Astroff and Safe 1990). 2,3,7,8-TCDD application also antagonized the treatment with estradiol. The authors concluded that 2,3,7,8-TCDD antagonized the estrogen-induced uterine response and that the Ah receptor was involved in mediating the reaction. Other authors suggest that the anti-estrogen effect is mediated by 2,3,7,8-TCDD-induced metabolism of estrogens (Gierthy et al. 1987).

In non-pregnant female rats, decreases in ovarian weight, estrous cyclicity, ovulation rate, and the number of ova released were observed following a single dose of 2,3,7,8-TCDD (Li et al. 1995a, 1995b). Increases in LH and follicle stimulating hormone levels were also observed. The mechanisms involved in these

effects are thought to involve direct effects on the ovaries and effects on the hypothalamus/pituitary axis. The normal preovulatory surge of LH was not observed in the 2,3,7,8-TCDD-exposed rats, suggesting that 2,3,7,8-TCDD inhibited the positive feedback action of 17β-estradiol at the hypothalamic-pituitary axis (Li et al. 1995a). In hypophysectomized rats, 2,3,7,8-TCDD exposure resulted in a reduction of ovulation; Li et al. (1995a) suggests that this may be the result of a direct effect on the ovary, although the mechanism has not been elucidated.

Endometriosis has been observed in monkeys chronically exposed to 2,3,7,8-TCDD in the diet (Rier et al. 1993). A possible association between 2,3,7,8-TCDD and endometriosis is supported by rat and mouse studies using surgically induced models of endometriosis (Cummings et al. 1996; Johnson et al. 1997). In contrast, Foster et al. (1997) found that 2,3,7,8-TCDD exposure diminished endometrial tissue growth in mice. These studies used different models of surgically induced endometriosis and highlight the complexity of the disease. In the Cummings et al. (1996) and Johnson et al. (1997) studies, the animals were exposed to 2,3,7,8-TCDD prior to the development of endometriosis, and immune suppression probably facilitated the growth of endometrial tissue. In the Foster et al. (1997) model, 2,3,7,8-TCDD was administered after endometriosis development and 2,3,7,8-TCDD, via its anti-estrogenic effects, inhibited tissue growth. The relationship between CDD exposure and endometriosis in humans has not been adequately studied. In humans, the etiology of endometriosis likely involves a complex interplay between a number of diverse physiological factors including altered cell-mediated immunity and increased levels of growth hormone.

Although the human data regarding reproductive effects are inconsistent, a number of reproductive effects have been observed in animals, including deceased fertility, altered hormone levels, and gonad damage in males and females. The similarity between some of the effects observed in humans and animals suggest that reproductive effects may also occur in humans.

Developmental Effects. The developmental toxicity of 2,3,7,8-TCDD has been investigated in several human populations, with conflicting results. Most studies did not find increases in the number of birth defects in the children of men exposed to 2,3,7,8-TCDD in a chlorophenols manufacturing facility (Townsend et al. 1982) or during the Vietnam war (Aschengrau and Monson 1990; Erickson et al. 1984; Wolfe et al. 1995); or the children of parents living in Seveso, Italy (Bisanti et al. 1980; Mastroiacovo et al. 1988). Some studies did find increases in the incidence of specific defects (e.g., talipes, ventricular septal defect) in the infants of exposed fathers or mothers and fathers (Aschengrau and Monson 1990; Erickson et al. 1984; Hanify et al. 1981; Wolfe et al. 1995), but there was little consistency regarding the

type of defect or the target organ/system. The lack of exposure data, small sample sizes, and the lack of reliable data for birth defect rates prior to 2,3,7,8-TCDD exposure precludes drawing conclusions from these human studies. A section below summarizes information on health effects in humans associated with exposure to CDDs *in utero* and/or via breast milk.

Developmental toxicity has been observed in rats, mice, rabbits, hamsters, and monkeys exposed to 2,3,7,8-TCDD and other CDD congeners. Perinatal exposure to 2,3,7,8-TCDD results in structural malformations, functional alterations, decreased growth, and fetal/newborn mortality. Many of the effects occurred at 2,3,7,8-TCDD doses which were not maternally toxic. Acute oral exposure to 2,3,7,8-TCDD during gestation caused an increased incidence of cleft palate and skeletal anomalies in offspring of rats (Giaviani et al. 1983; Huuskonen et al. 1994), mice (Abbott and Birnbaum 1989a; Courtney 1976; Dasenbrock et al. 1992; Neubert and Dillman 1972; Smith et al. 1976; Weber et al. 1985), and rabbits (Giavini et al. 1983). These effects were also observed in fetuses of mice that received subcutaneous injections of 2,3,7,8-TCDD during gestation (Courtney 1976; Poland and Glover 1980). The 2,3,7,8-TCDD-induced cleft palate is caused by the failure of the opposing palatal shelves to fuse (Pratt et al. 1984); 2,3,7,8-TCDD does not alter the size of the palatal shelves or interfere with the opposing shelves coming into contact. Under normal conditions, there is a cessation of medial cell proliferation, a degeneration of peridermal medial cells, and a transformation of basal cells to mesenchymal cells as the opposing palatal shelves come into contact and fuse (Abbott and Birnbaum 1989b). 2,3,7,8-TCDD exposure alters medial cell proliferation and differentiation resulting in the formation of stratified squamous epithelium. Abbott and Birnbaum (1990a) suggest that the altered proliferation and differentiation of the medial cells is due to 2,3,7,8-TCDD-induced reductions of several growth factors (EGF, TGF-α, and TGF-β1) and increases in EGF receptor expression. EGF and TGF-α (which both bind to the EGF receptor) stimulate epithelial proliferation and differentiation and TGF-β1 inhibits epithelial proliferation. The increased levels of EGF receptor appear to compensate for the decreased EGF and TGF-α levels resulting in continued proliferation. Abbott et al. (1994a, 1994b) suggest that the altered expression of growth factors may be mediated by the Ah receptor. Exposure to 2,3,7,8-TCDD resulted in a dose-dependent downregulation of the Ah receptor throughout the palate; this probably occurs at the transcriptional level as decreases in mRNA were also observed (Abbott et al. 1994b). There is no evidence for direct Ah regulation of growth factors; rather, transcriptional regulation of related genetic activity may indirectly influence growth factor expression. Data which support an association between Ah receptor and cleft palate include a correlation between 2,3,7,8-TCDD binding to the Ah receptor and altered growth factor expression (Abbott et al. 1994b); finding of 2,3,7,8-TCDD-induced altered Ah receptor expression

and altered growth factor expression at doses which do not induce cleft palate (Abbott et al. 1994b); and the inability of 2,3,7,8-TCDD to induce cleft palate in strains of mice which have low affinity for Ah receptors (Pratt et al. 1984; Silkworth et al. 1989b).

Kidney malformations, particularly hydronephrosis, were observed in the offspring of rats (Giavini et al. 1983; Huuskonen et al. 1994), mice (Abbott et al. 1987a, 1987b; Courtney 1976; Moore et al. 1973; Silkworth et al. 1989b), and hamsters (Gray et al. 1995) orally exposed to 2,3,7,8-TCDD during gestation. Kidney defects were also observed in mouse offspring following *in utero* subcutaneous exposure to 2,3,7,8-TCDD (Courtney 1976) and in mice postnatally exposed to 2,3,7,8-TCDD via contaminated mothers' milk (Couture-Haws et al. 1991b). The hydronephrosis observed in these offspring is the result of occlusion of the ureter and subsequent accumulation of urine in the kidney (Abbott et al. 1987a). Prenatal exposure to 2,3,7,8-TCDD results in hyperplasia of the epithelium in the ureter, obstruction of the ureteric lumen, and a restriction of the flow of urine. Abbott and Birnbaum (1990b) found that 2,3,7,8-TCDD interfered with the normal decline in EGF receptors in the ureteric epithelia, resulting in excessive proliferation. In the bladder, 2,3,7,8-TCDD exposure also resulted in an increase in the epithelial thickness and continued expression of EGF receptors. 2,3,7,8-TCDD also appears to directly damage the kidney. Under normal conditions, there is an increase in laminin and type IV collagen levels and a thickening of the *lamina densa* of the glomerular basement membrane, which is important in establishing the filtration barrier. Following exposure to 2,3,7,8-TCDD, there is a decreased expression of laminin and type IV collagen and a diminished thickening of the lamina densa (Abbott et al. 1987b). This immature filtration barrier is likely to result in proteinuria and may result in increased urine volume.

A number of recently published studies have shown that the developing reproductive system is very sensitive to the toxicity of 2,3,7,8-TCDD. In female rats, exposure to 2,3,7,8-TCDD on Gd 8 caused functional reproductive toxicity (accelerated onset of constant estrus, shortened reproductive lifespan, reduced ovarian weight, and cystic hyperplasia of the endometrium) (Gray and Ostby 1995). Although there were no effects on fertility or estrous cyclicity when 2,3,7,8-TCDD exposure occurred after organogenesis (exposure on Gd 15) (Gray and Ostby 1995), external urogenital malformations (clefting, hypospadias, vaginal thread, and delayed vaginal opening) were observed (Flaws et al. 1997; Gray and Ostby 1995; Gray et al. 1997a; Heimler et al. 1998). These malformations to external genitalia are likely to interfere with mating (Gray and Ostby 1995). The authors note that the effects on the external genitalia are similar to effects observed in animals exposed to potent estrogen-like chemicals (e.g., DES, estradiol), although it likely that these effects occur by a different mechanism.

In male rats, perinatal exposure to 2,3,7,8-TCDD resulted in alterations in androgen status (decreased plasma testosterone levels, delay in testes descent, delay in external signs of puberty, and decreased ventral prostate and seminal vesicle weights), testes and cauda epididymis weights, and spermatogenesis (decreased daily sperm production, amount of mature sperm in cauda epididymis, and amount of sperm ejaculated), and in demasculinization and partial feminization of sexual behavior following exposure on Gd 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Gray et al. 1995; 1997b; Mably et al. 1992a, 1992b, 1992c; Sommer et al. 1996). In most of these studies, the experimental protocol involved gavaging the dams with a single dose of 2,3,7,8-TCDD on Gd 8 (Gray et al. 1995) or 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Gray et al. 1995; Mably et al. 1992a, 1992b, 1992c) and assessing a number of indices of reproductive development and function in newborn, juvenile, pre-pubescent, post-pubescent, and mature male rats. Because 2,3,7,8-TCDD is lipophilic and has a relatively long half-life, a single dose on Gd 15 will result in transplacental exposure from Gd 15 to birth and exposure via contaminated milk. Bjerke and Peterson (1994) compared the reproductive effects of 2,3,7,8-TCDD in rats exposed *in utero* to the effects observed in rats exposed to 2,3,7,8-TCDD only during lactation. Both *in utero* and lactational exposure resulted in decreased plasma testosterone level, decreased seminal vesicle and ventral prostate growth, and decreased epididymal sperm reserves. Exposure *in utero* only also resulted in decreased daily sperm production and delayed puberty; and exposure by lactation only resulted in partial feminization of sexual behavior. These data suggest that the timing of the 2,3,7,8-TCDD exposure is important. The mechanism by which 2,3,7,8-TCDD disrupts the development of the reproductive system and whether all of the reproductive effects have similar mechanisms is not known. Early investigators of the effects of 2,3,7,8-TCDD on sexual behavior suggested that perinatal exposure to 2,3,7,8-TCDD resulted in impaired sexual differentiation of the central nervous system (Mably et al. 1992b). The results of the Bjerke et al. (1994b) study suggest that the 2,3,7,8-TCDD-induced alterations in sexual behavior were not due to 2,3,7,8-TCDD acting as an estrogen antagonist or altering ER capacities of hypothalamic nuclei. The volume of the sexually dimorphic nucleus in the preoptic area of the hypothalamus (SDN-POA), which is dependent upon testosterone-derived estradiol in the brain during perinatal development, was not altered in 2,3,7,8-TCDD-exposed rats. Additionally, the sexual differentiation of ER concentration in brain nuclei which exhibit sexual dimorphism (ventromedial nuclei, medial preoptic nuclei, bed nucleus of the stria terminalis, periventricular preoptic area nucleus, cortical and medial amygdala, and arcuate nucleus) were not affected by 2,3,7,8-TCDD. Thus, 2,3,7,8-TCDD effects did not parallel those of either estrogen or androgen antagonists. Gray et al. (1995) also support the theory that 2,3,7,8-TCDD does not interfere with testosterone- and estrogen-dependent central nervous system sexual differentiation. In their study, no alterations in mounting behavior were observed in male hamsters perinatally exposed to 2,3,7,8-TCDD (in

hamsters, masculinization of the central nervous system requires perinatal exposure to testosterone). Bjerke et al. (1994b) proposed that 2,3,7,8-TCDD may affect other systems, such as brain amine content or growth factor expression of function, which would indirectly impact sexual differentiation. Similarly, Gray et al. (1995) suggested that 2,3,7,8-TCDD-induced alterations in the growth factors and receptors involved in urogenital system cell differentiation and proliferation may result in alterations in morphological sexual differentiation. Bjerke et al. (1994a) also found that the 2,3,7,8-TCDD-induced inhibition of ventral prostate weight and protein content imprinting was not due to perinatal reductions in plasma androgen levels because no effect on imprinting of the seminal vesicle, penis, or pituitary were observed in the 2,3,7,8-TCDD-exposed rats. Using a treatment regime that consisted of administration of a loading subcutaneous dose of 2,3,7,8-TCDD to female rats prior to mating, followed by weekly maintenance subcutaneous doses during mating, pregnancy, and lactation, Faqi et al. (1998) reported that sperm parameters were the most susceptible end points in male offspring examined at puberty (70 days old) and adulthood (170 days old). Based on pharmacokinetic considerations, the authors estimated that the lowest effective dose was <0.8 ng/kg/day. The sperm parameters that were altered were sperm number from cauda epididymis, daily sperm production, sperm transit rate, and percent abnormal sperm (more so in adults than in pubertal rats). No significant and/or consistent effects were observed on litter size, sex ratio, body weights, developmental landmarks, weight of sex organs, and sexual behavior. Testosterone levels were significantly reduced at age 170 days but not at age 70 days. In spite of sperm alterations, all exposed males exhibited normal reproductive performance and successfully impregnated untreated female to produce viable fetuses.

Recent studies have also focused on the role of the Ah receptor in the 2,3,7,8-TCDD-induced alterations in the development of the male reproductive system. Roman et al. (1998a) recently demonstrated the presence of both the Ah receptor and the receptor nuclear translocator (Arnt) in the testis, epididymis, vas deferens, ventral and dorsolateral prostate, and seminal vesicles from adult Holtzman rats. Arnt was localized in all organs in a variety of cell types; subcellular localization varied across organs and cell types within these organs. Unfortunately, technical difficulties precluded the evaluation of the Ah receptor distribution in the various organs. The authors also showed that a single oral dose of 25 µg 2,3,7,8-TCDD/kg produced significant induction of CYP1A1 in the ventral and dorsolateral prostate. CYP1A1 expression was localized in the epithelial cells of the ventral and lateral lobes of the prostate. Less CYP1A1 induction was seen in selected epithelial cells from other tissues, and no induction was detected in the testis. Also, 2,3,7,8-TCDD had no effect on Arnt protein expression, but Ah receptor expression was significantly reduced in all organs examined. In another study from this series, Roman and Peterson (1998) found that,

relative to controls, *in utero* exposure to 2,3,7,8-TCDD (1 µg/kg) transiently decreased the amount of several prostate-specific androgen-regulated mRNAs, all of which are markers of a differentiated ductal epithelium. This was in contrast with observations in adults, in which 2,3,7,8-TCDD induced CYP1A1 mRNA without altering the amount of prostate-specific, androgen-regulated mRNAs. These results suggested that the developing prostate can directly respond to *in utero* and lactational exposure to 2,3,7,8-TCDD, and that this exposure not only impairs prostate growth but also delays prostate luminal epithelial cell differentiation. In yet an additional study from this series, Roman et al. (1998b) reported that in the most severely affected animals, 2,3,7,8-TCDD produced alterations in the histological arrangement of epithelial and stromal cells and in the spatial distribution of androgen receptor expression.

Other developmental effects that have been observed in animals include immunotoxicity (thymic atrophy, immunosuppression, and alterations in thymocyte phenotypes) (Fine et al. 1989; Gehrs et al. 1997a, 1997b; Håkansson et al. 1987; Huuskonen et al. 1994; Luster et al. 1980; Madsen and Larsen 1989; Thomas and Hinsdill 1979), decreased fetal and newborn body weight (Abbott et al. 1992; Bjerke et al. 1994a; Bjerke and Peterson 1994), fetal/newborn mortality or decreased survival (Bjerke et al. 1994a; Bjerke and Peterson 1994; Huuskonen et al. 1994; McNulty 1984; Murray et al. 1979; Nau et al. 1986), and altered social behavior (Schantz et al. 1992).

Developmental toxicity has also been observed in animals exposed to other CDDs. These effects include heart defects in rats exposed to 2,7-DCDD (Schwetz et al. 1973); decreased thymic weight in rats exposed to 1,2,3,7,8-PCDD (Madsen and Larsen 1989); subcutaneous edema, decreased fetal growth, delayed ossification, dilated renal pelvis, and cleft palate in rats exposed to HxCDD (Schwetz et al. 1973); and subcutaneous edema in rats exposed to OCDD (Schwetz et al. 1973).

The animal database provides strong evidence that developmental toxicity is a sensitive end point following 2,3,7,8-TCDD exposure. Structural malformations, functional alterations (including impaired development of reproductive system), decreased growth, and fetal/newborn mortality have been observed in several animal species. Limited human data on the developmental toxicity of CDDs is available. Most of these studies examined the occurrence of birth defects in children of males exposed to 2,3,7,8-TCDD. Deficiencies in the human data preclude drawing firm conclusion on the potential of 2,3,7,8-TCDD to induce developmental effects in humans. However, the animal data suggest that 2,3,7,8-TCDD is a likely human developmental toxicant.

Health Effects Associated with Exposure to CDDs in Breast Milk. The developing organism is very susceptible to the toxicity of CDDs, in particular 2,3,7,8-TCDD. Prenatal or perinatal exposure has resulted in structural malformations (e.g., cleft palate, hydronephrosis), functional alterations (e.g., damage to the immune system, impaired development of the reproductive system), decreased growth, and fetal/newborn mortality in several animal species. Additionally, several animal studies (summarized in Table 2-14) provide evidence that lactation-only exposure to 2,3,7,8-TCDD can adversely affect the developing animal. Impaired development of the reproductive system (Bjerke and Peterson 1994), increased incidence of hydronephrosis (Couture-Haws et al. 1991a, 1991b), decreased weight gain, thymic atrophy (Faith and Moore 1977; Håkansson et al. 1987), and suppression of cell-mediated immunity (Faith and Moore 1977) have been observed in rats and mice exposed to 2,3,7,8-TCDD during lactation but not during gestation. The authors of these studies noted that most of the effects observed following lactation-only exposure were similar to those observed in animals exposed to 2,3,7,8-TCDD during gestation.

Because CDDs are efficiently absorbed following ingestion of breast milk (approximately 95% absorption efficiency for most congeners, see Section 2.3.4.4 for more information) and animal studies have found that lactation-only exposure can result in developmental effects, there is concern that breast-fed infants of women with high background levels of CDDs may be at risk. Ayotte et al. (1996) predicted that exposure to CDDs and related chemicals from breast milk will strongly influence the body burden of these chemicals during childhood and adolescence. Several human studies have examined the possible association between background CDD and CDF levels from *in utero* exposure and exposure from breast milk, and adverse health effects in infants. These studies (summarized in Table 2-15) found alterations in the levels of some markers of liver function (plasma ALT and AST) (Pluim et al. 1994a), thyroid function (thyroxine, thyroid stimulating hormone) (Koopman-Esseboom et al. 1994; Pluim et al. 1993b), and immune function (T-cell markers [TcR$\gamma\delta^+$, $CD3^+CD8^+$, and TcR$\alpha\beta^+$] and monocyte) (Weisglas-Kuperus et al. 1995), and the neurological optimality score in infants (Huisman et al. 1995a) which significantly correlated with CDD and CDF TEQ levels in breast milk. In follow-up studies and studies of older infants or children, no relationship between high levels of CDDs, CDFs, and PCBs in breast milk and neurological development, neurological optimality score, and/or reflexes was found at ages 6 (Pluim et al. 1996), 18 (Huisman et al. 1995b), or 31 months (Ilsen et al. 1996). Although the Ilsen et al. (1996) study of 31-month-old children did not find any alterations in overall neurological optimality or suboptimality scores, significant alterations, indicative of enhanced neuromuscular maturation and higher reflexes, were found in some tests (results were still within the normal range). Hypomineralization of teeth was found in 6- to 7-year-old children who

Table 2-14. Health Effects in Animals Following Lactation-Only Exposure to 2,3,7,8-TCDD

Health effect	Orally administered maternal dose of 2,3,7,8-TCDD	Reference
Feminization of sexual behavior, decreased plasma testosterone concentration, decreased ventral prostate and seminal vesicle weight, protein and DNA content, and decreased sperm reserves in male Holtzman rats	1 µg/kg on gestation day 15 (cross fostered)	Bjerke and Peterson 1994b
Increased incidence of hydronephrosis in newborn C57BL/6N mice	3 or 12 µg/kg on gestation day 6 (cross fostered)	Couture-Haws et al. 1991a
Increased incidence of hydronephrosis in newborn C57BL/6N mice	3 or 12 µg/kg on postnatal day 1 or 4	Couture-Haws et al. 1991b
Decreased weight gain, liver enlargement, thymus atrophy, and reduced ability to store vitamin A in young Sprague Dawley rats	10 µg/kg on postnatal day 0	Häkansson et al. 1987
Decreased body weight and thymic atrophy in 25- and 39-day old F344 rats, and suppression of cell-mediated immunity in young rats	5 µg/kg/day on postnatal days 0, 7, and 14	Faith and Moore 1977

Table 2-15. Health Effects in Humans Associated with CDD and CDF Levels in Breast Milk

Health effect	Levels of CDD and CDF in breast milk (ng TEQ/kg milk fat)	Reference
Increased plasma AST and ALT activities and decreased platelet levels correlated with increased cumulative CDD and CDF intake in 11-week-old infants. No effect on plasma GGT activity or plasma cholesterol, total and conjugated bilirubin, or leukocyte levels	8.7–62.7 (mean of 28.1); cumulative intake: 5.7–123.7 ng TEQ (mean of 44.7)	Pluim et al. 1994a
Increased total thyroxine level, thyroid stimulating hormone level, and ratio of total thyroxine level to thyroxine binding globulin level in 11-week-old infants in high-exposure group	High-exposure group: 37.5 Low-exposure group: 18.6	Pluim et al. 1993b
Increased thyroid stimulating hormone level in breastfed infants aged 2 weeks or 3 months. Lower total thyroxine levels and higher thyroid stimulating hormone levels in high exposure group	12.44–76.43 (mean of 32.06) high-exposure group: >30.75 low-exposure group: ≤30.75 ng	Koopman-Esseboom et al. 1994
Increased T-cell marker (TcRγδ$^+$) in newborns correlated with TEQ for CDDs and CDFs in breast milk. Decreased monocyte level in 3-month -olds correlated with TEQ for CDDs and CDFs in breast milk and cumulative TEQ intake for CDDs, CDFs, and dioxin-like PCBs (concentration in breast milk x number of days of breast feeding) Increased T-cell markers (CD3$^+$CD8$^+$ and TcRαβ$^+$) in 18-month olds correlated with TEQ for CDDs and CDFs in breast milk, but not with cumulative TEQ intake	Not reported	Weisglas-Kuperus et al. 1995
Decreased neurological optimality score in newborns correlated with breast milk concentration of 1,2,3,7,8-PCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, and 1,2,3,4,6,7,8-HpCDD	Breast milk levels (median concentration): 1,2,3,7,8-PeCDD=10.25, 1,2,3,4,7,8-HxCDD=8.71, 1,2,3,6,7,8-HxCDD=45.98, 1,2,3,7,8,9-HxCDD=6.72, and 1,2,3,4,6,7,8-HpCDD=57.38 ng/kg fat	Huisman et al. 1995a
No adverse effect on neurological development, neurological optimality score, number of abnormal reflexes, or tonus score at 6 months of age	high-exposure group: 29.2-62.7 (mean= 37.4) ng TEQ/kg low-exposure group: 8.7-28.0 (mean= 18.1) ng TEQ/kg	Pluim et al. 1996

Table 2-15. Health Effects in Humans Associated with CDD and CDF Levels in Breast Milk (continued)

Health effect	Levels of CDD and CDF in breast milk (ng TEQ/kg milk fat)	Reference
No adverse effect on neurological optimality score at 18 months of age	(same children as Huisman et al. 1995a)	Huisman et al. 1995b
No adverse effect on overall neurological optimality or suboptimality scores at 31 months of age. Some alterations in individual test scores which were indicative of enhanced neuromuscular maturation and higher reflexes (altered test scores were within normal range)	high-exposure group: median concentration of 67.7 ng TEQ low-exposure group: median=13.7 ng TEQ	Ilsen et al. 1996
Increase in frequency and severity of hypomineralization of teeth in 6–7-year-old children	high-exposure group: >16.0 pg TEQ/g milk fat medium-exposure group: 8.0-16.0 pg TEQ/g low-exposure group: <8.0 pg TEQ/g	Alaluusua et al. 1996
No correlation between birth weight of primiparae children and CDD and CDF TEQ levels in breast milk	10.8-96.3 pgTEQ/g fat	Vartiainen et al. 1998
No adverse effect on birth weight, body weight and head circumference at ages 1, 10, or 26 weeks, growth weight, or liver size	high-exposure group: 29.2-62.7 (mean= 37.4) ng TEQ/kg low-exposure group: 8.7-28.0 (mean= 18.1) ng TEQ/kg	Pluim et al. 1996
No correlation between decarboxylated prothrombin and vitamin K levels in 11 week old infants and CDD and CDF TEQ levels in breast milk	13.7–62.6 (mean of 29.4)	Pluim et al. 1994b
2,3,7,8-TCDD content of total breast milk was significantly higher in 4 of 14 mothers with children exhibiting abnormal bleeding	Breast milk level of 2,3,7,8-TCDD: 5.35–17.0 ng/kg milk fat (mean of 9.79)	Koope et al. 1991

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEQ = toxicity equivalency

received higher than background levels of CDDs and CDFs in breast milk (Alaluusua et al. 1996). Other studies have not found a relationship between higher background levels of CDDs, CDFs, and PCBs in breast milk and adverse health effects (summarized in Table 2-15); decarboxylated prothrombin and vitamin K levels in 11-week-old infants (Pluim et al. 1994b); birth weight (Pluim et al. 1996; Vartiainen et al. 1998), head circumference, and body weight at 1, 10, and 26 weeks of age (Pluim et al. 1996); or liver size (Pluim et al. 1996) were not adversely affected. Although significant correlations were found, the data should be interpreted cautiously because the levels of these markers were within the normal range and the correlation coefficients were low suggesting that only a small amount of the variance in the marker concentrations can be attributed to CDD and CDF levels.

The animal data suggest that lactation-only exposure to relatively high concentrations of CDDs can result in serious health effects. However, the human data show that the risk of CDD-induced health effects in infants exposed to background levels of CDDs and CDFs in breastmilk is small and this risk, in most cases, does not outweigh the benefits of breast-feeding.

Genotoxic Effects. *In vivo* genotoxicity studies are summarized in Table 2-16. Human studies have been conducted on populations exposed to 2,3,7,8-TCDD. An increased incidence of chromosomal aberrations was found in the fetal tissues, but not in the maternal tissues, following induced abortions in a group of women exposed to 2,3,7,8-TCDD in the Seveso accident (Tenchini et al. 1983). However, cases treated for chloracne in the area did not have an elevated frequency of chromosomal aberrations (Reggiani 1980). Results of a higher incidence of chromosomal aberrations were inconsistent in groups of Vietnam veterans (Kaye et al. 1985) or no cytogenetic changes were reported (Mulcahy et al. 1980). Fewer birth defects due to chromosomal abnormalities in children of Vietnam veterans were reported in another study (Erickson et al. 1984). Human studies cited above were limited by several factors. Generally, the levels of exposure to 2,3,7,8-TCDD were not known and coexposure to other potentially active compounds occurred in all studies. In the case of Vietnam veterans, a long postexposure period passed before the cytogenetic analysis was done. Furthermore, most of the studies used groups that were too small (less than 20 individuals) to have the statistical power to detect any changes.

Table 2-16. Genotoxicity of 2,3,7,8-TCDD *In Vivo*

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Recessive lethals	–	Zimmering et al. 1985
Rats, bone marrow	Chromosomal aberrations	–	Loprieno et al. 1982
Mice, bone marrow	Chromosomal aberrations	+	Loprieno et al. 1982
Rats, bone marrow	Chromosomal aberrations	+	Green et al. 1977
Mice, bone marrow	Chromosomal aberrations, SCE, micronucleus test	–	Meyne et al. 1985
Monkeys, peripheral lymphocytes	Chromosomal aberrations, SCE	–	Lim et al. 1987
Rats	Dominant lethals	–	Khera and Ruddick 1973
Rats, liver	DNA adducts	–	Randerath et al. 1989
Rats, liver	DNA-single strand breaks	+	Wahba et al. 1989
Rats, liver	DNA adducts	–	Poland and Glover 1979
Human, aborted tissues	Chromosomal aberrations	+	Tenchini et al. 1983
Human, peripheral lymphocytes	Chromosomal aberrations	–	Reggiani 1980
Human, peripheral lymphocytes	Chromosomal aberrations	+	Kaye et al. 1985
Human, peripheral lymphocytes	Chromosomal aberrations	–	Mulcahy et al. 1980
Human, peripheral lymphocytes	Chromosomal aberrations, SCE	–	Zober et al. 1993

– = negative result; + = positive result; DNA = deoxyribonucleic acid; SCE = sister chromatid exchanges

In a study in which current 2,3,7,8-TCDD blood levels of previously exposed workers were approximately 25 times higher than in referents, there was no evidence of increased incidence of chromosomal aberrations or sister chromatid exchanges (Zober et al. 1993).

Animal studies on the genotoxicity of CDDs are inconclusive. When Osborne-Mendel rats were given 2,3,7,8-TCDD (0.25, 0.5, 1, 2, or 4 µg/kg) by gavage twice a week for 13 weeks, increased incidence of chromosomal aberrations was observed in the highest-exposure group (Green et al. 1977). Increased incidences of gaps and chromatid aberrations were observed in bone marrow cells of CD-1 mice following an intraperitoneal injection of 10 µg/kg 2,3,7,8-TCDD (Loprieno et al. 1982). Positive results were obtained at 96 hours, but not 24 hours, posttreatment. In contrast, no induction of structural chromosomal changes was found in CD-COBS rats orally exposed to 1.0, 0.1, or 0.01 µg/kg 2,3,7,8-TCDD once a week for 45 weeks (Loprieno et al. 1982). In addition, no differences in the frequency of sister chromatid exchanges and chromosomal aberrations in peripheral lymphocytes were observed in a group of rhesus monkeys receiving 0.001 µg/kg 2,3,7,8-TCDD in the feed for 4 years and their matching controls (Lim et al. 1987). Furthermore, no induction of chromosomal aberrations or sister chromatid exchanges, or increases in the frequency of micronuclei, were found in bone marrow cells of C57BL/6J (with high-affinity 2,3,7,8-TCDD receptor) or DBA/2J mice (with low-affinity 2,3,7,8-TCDD receptor) following a single intraperitoneal injection of 2,3,7,8-TCDD at doses of 50, 100, or 150 µg/kg (Meyne et al. 1985). The samples were examined within 8–48 hours. The negative results may, however, have been due to the time-dependent detectability of chromosomal changes after CDD exposure reported earlier (Loprieno et al. 1982).

In addition to studies dealing with structural chromosomal changes, effects on DNA were also investigated. Oral exposure to 1 µg/kg/week of 2,3,7,8-TCDD or 1,2,3,7,8-PCDD for up to 6 months did not increase the formation of DNA adducts in Sprague-Dawley rats (Randerath et al. 1989). A single oral dose of 2,3,7,8-TCDD (25–100 µg/kg) caused time-dependent increases in the induction of DNA single-strand breaks (and lipid peroxidation) in hepatic cells of Sprague-Dawley rats terminated within 3–14 days after the treatment (Wahba et al. 1989).

Negative results were obtained in reproductive tests including a dominant-lethal test following 7 daily oral doses of 2,3,7,8-TCDD (4, 8, or 12 µg/kg/day) to male Wistar rats (Khera and Ruddick 1973) and a sex-linked recessive-lethal test with 2,3,7,8-TCDD in *Drosophila melanogaster* (Zimmering et al. 1985).

In vitro genotoxicity studies are summarized in Table 2-17. Eukaryotic cell systems were used for detecting the effects of 2,3,7,8-TCDD exposure on DNA. Exposure to 2,3,7,8-TCDD did not stimulate the unscheduled DNA synthesis in cultural human cells (Loprieno et al. 1982), but inhibited DNA, ribonucleic acid (RNA), and protein synthesis in mouse lymphocytes (Luster et al. 1979); caused gene mutations in mouse lymphoma cells (Rogers et al. 1982); and induced sister chromatid exchanges in Chinese hamster cells (Toth et al. 1984).

Several researchers used the Ames test with *Salmonella typhimurium* to assess the mutagenicity of 2,3,7,8-TCDD in prokaryotic organisms. Predominantly negative results were obtained with tester strains G46, TA 1530, TA 1535, TA 100, TA 1950, and TA 1975, revealing base pair substitutions; and with strains TA 1531, TA 1532, TA 1534, TA 1538, TA 98, and TA 1978, revealing frame shift mutations (Geiger and Neal 1981; Gilbert et al. 1980; Mortelmans et al. 1984; Toth et al. 1984). However, some of the studies were limited by using 2,3,7,8-TCDD concentrations in excess of its solubility in water. Only two early studies reported positive results (Hussain et al. 1972; Seiler 1973). However, the results were limited by failure to demonstrate a dose-response relationship and by low bacterial survival rates. In addition, 2,3,7,8-TCDD exposure induced reverse mutations in *Escherichia coli* (Hussain et al. 1972) and in *Saccharomyces cerevisiae* (Bronzetti et al. 1983). The conflicting data obtained in the above studies may result from technical difficulties in testing 2,3,7,8-TCDD rather than from a lack of biological activity. Testing difficulties arise from an extreme insolubility of this compound and a high toxicity observed in some test systems, which would be anticipated to result in a very narrow window for effective genotoxic doses.

Considering the inconclusive results reported above and the severe limitations of some studies, there is no strong evidence for 2,3,7,8-TCDD genotoxicity. The information regarding the mutagenic potential of other CDDs is even more limited.

Cancer. Numerous epidemiological studies investigated the effects of 2,3,7,8-TCDD exposure on the development of cancer. A number of large-scale retrospective cohort mortality studies (Becher et al. 1996; Fingerhut et al. 1991; Hooiveld et al. 1998; Kogevinas et al. 1993, 1997; Manz et al. 1991; Ott and Zober 1996; Zober et al. 1990) have found significant increases in cancer mortalities (all types of cancers combined). These increases were typically found in the highest exposed workers and in workers with the longest latency periods. In general, the SMRs were low (less than 1.5); however, the high degree of consistency between studies suggests that the increases in mortalities were not due to chance. The possible

Table 2-17. Genotoxicity of 2,3,7,8-TCDD *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium				
TA 1530	Reverse mutations	NA	–	Hussain et al. 1972
TA 1532	Reverse mutations	NA	+	Hussain et al. 1972
TA 1535	Reverse mutations	NA	–	Seiler 1973
TA 1531	Reverse mutations	NA	–	Seiler 1973
TA 1532	Reverse mutations	NA	(+)	Seiler 1973
TA 1537	Reverse mutations	NA	(+)	Seiler 1973
TA 1535	Reverse mutations	–	NA	Geiger and Neal 1981
TA 100	Reverse mutations	–	NA	Geiger and Neal 1981
TA 1537	Reverse mutations	–	–	Geiger and Neal 1981
TA 1538	Reverse mutations	–	NA	Geiger and Neal 1981
TA 98	Reverse mutations	–	NA	Geiger and Neal 1981
TA 100	Reverse mutations	–	NA	Mortelmans et al. 1984
TA 1535	Reverse mutations	–	NA	Mortelmans et al. 1984
TA 1537	Reverse mutations	–	NA	Mortelmans et al. 1984
TA 98	Reverse mutations	–	NA	Mortelmans et al. 1984
TA 1530	Reverse mutations	–	NA	Gilbert et al. 1980
TA 1535	Reverse mutations	–	NA	Gilbert et al. 1980
TA 100	Reverse mutations	–	NA	Gilbert et al. 1980
TA 1537	Reverse mutations	–	NA	Gilbert et al. 1980

Table 2-17. Genotoxicity of 2,3,7,8-TCDD *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
TA 1538	Reverse mutations	–	NA	Gilbert et al. 1980
TA 98	Reverse mutations	–	NA	Gilbert et al. 1980
TA 1535	Reverse mutations	–	–	Toth et al. 1984
TA 100	Reverse mutations	–	–	Toth et al. 1984
TA 1537	Reverse mutations	–	–	Toth et al. 1984
TA 1538	Reverse mutations	–	–	Toth et al. 1984
TA 98	Reverse mutations	–	–	Toth et al. 1984
Escherichia coli	Reverse mutations	NA	–	Hussain et al. 1972
Saccharomyces cerevisiae	Reverse mutations	+	–	Bronzetti et al. 1983
S. cerevisiae	Gene conversion	+	–	Bronzetti et al. 1983
S. cerevisiae	Host mediated assay	+	–	Bronzetti et al. 1983
Eukaryotic organisms: EUE human cells	UDS	NA	–	Loprieno et al. 1982
Mouse lymphocytes	DNA, RNA synthesis inhibition	NA	–	Luster et al. 1979
L51784 mouse lymphoma cells	Gene mutations	NA	+	Rogers et al. 1982
Chinese hamster cells	SCE	–	+	Toth et al. 1984

– = negative result; + = positive result; (+) = weakly positive result; NA = not applicable; RNA = ribonucleic acid; SCE = sister chromatid exchanges; UDS = unscheduled DNA synthesis; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

risks of several specific types of cancer have also been found, but the data are somewhat inconsistent. The site-specific cancers with elevated possible risks include soft-tissue sarcoma (Eriksson et al. 1981, 1990; Fingerhut et al. 1991; Hardell and Eriksson 1988; Hardell and Sandrom 1979; Hardell et al. 1995; Kogevinas et al. 1995, 1997; Saracci et al. 1991; Smith et al. 1984a), non-Hodgkin's lymphoma or malignant lymphoma (Becher et al. 1996; Cantor 1982; Hardell et al. 1981; Kogevinas et al. 1995), respiratory tract cancer (Fingerhut et al. 1991; Kogevinas et al. 1997; Manz et al. 1991; Zober et al. 1990), and gastrointestinal organ cancers (Axelson et al. 1980; Thiess et al. 1982). Furthermore, an increased risk of benign systemic neoplasms was reported in Vietnam Air Force veterans involved in Operation Ranch Hand (USAF 1991). There is some uncertainty regarding the interpretation of the epidemiology study results. In most studies, the cohort was also exposed to chemicals other than 2,3,7,8-TCDD and exact levels of exposure were not known. Furthermore, in some studies the exposure data were based solely on questionnaires and some recall bias could have been present. Other studies suffered from examining small cohorts or investigating the effects after a short latency period. The long latency period is important for detecting increases in soft-tissue sarcomas, presumably a major cancer outcome of CDD exposure in humans.

Several studies provided evidence of CDD-related carcinogenicity in animals. In general, the effects were dependent on the congener, species, sex, and route of administration, and were seen at doses that were close to doses that are toxic in the same animal species. Intermediate- and chronic-duration oral exposure to 2,3,7,8-TCDD induced multiple-site carcinomas and/or sarcomas in rats (Kociba et al. 1978a; NTP 1982b) and mice (Della Porta et al. 1987; NTP 1982a, 1982b; Toth et al. 1979). Similarly, chronic oral exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD induced carcinomas in mice and rats (NCI/NTP 1980), and exposure to 2,7-DCDD caused carcinomas and sarcomas in mice (NCI/NTP 1979a). However, no cancer effects were found following chronic exposure to 2,7-DCDD in rats (NCI/NTP 1979a). Furthermore, squamous cell carcinoma developed in hamsters (Rao et al. 1988) following intermediate-duration intraperitoneal exposures.

Short-term dermal studies with 2,3,7,8-TCDD had controversial results. Some studies reported its inhibitory effects on the development of skin tumors in mice otherwise initiated by 13-dimethylbenz-(*o*)anthracene (Berry et al. 1978, 1979). Others cited its ability to promote tumors initiated by N-methyl-N-nitro-N-nitrosoguanidine (Hebert et al. 1990; Poland et al. 1982). Further, intraperitoneal injection of 2,3,7,8-TCDD given 2 days prior to or concurrently with methylcholanthrene did not affect methyl-cholanthrene-induced carcinogenicity in C57BL/6 mice (Kouri et al. 1978); in contrast, 2,3,7,8-TCDD

pretreatment (intraperitoneal or subcutaneous) of DBA/2 mice slightly increased the carcinogenic index. In support of these data, promotion of GGT-positive hepatic foci and/or development of tumors was observed after initiation with nitrosodiethylamine in rats (Flodstrom and Ahlborg 1989; Flodstrom et al. 1991; Pitot et al. 1980) that were injected with 2,3,7,8-TCDD for an intermediate duration. A recent study of the promoting activity of 2,3,7,8-TCDD in the liver from female Sprague-Dawley rats showed that increased tissue burden of 2,3,7,8-TCDD, which correlated with increased CYP1A1 activity, did not necessarily lead to increased cell proliferation (Walker et al. 1998). Experimentally, cell proliferation was increased after 30 or more weeks of treatment, but not after only 14 weeks of treatment, whereas both tissue burden and CYP1A1 activity exhibited similar significant increases at both time points. Walker et al. (1998) noted that a dose metric such as the area under the curve, which measures total dose over time, did not correspond to either 2,3,7,8-TCDD-induced changes in cell proliferation or changes in CYP1A1 expression. This, according to the authors, suggested that for a number of 2,3,7,8-TCDD-induced responses, particularly those involving integrated signal transduction pathways such as altered cell/tissue growth and differentiation, dose metrics that incorporate not only magnitude of exposure, but also duration of exposure and temporal windows of sensitivity for the response, may be more appropriate.

The available data provided sufficient evidence that 2,3,7,8-TCDD is a carcinogen in animals and its action is not solely dependent upon initiation by other substances. This is in conflict with the inconclusive genotoxicity data. Significant binding of radioactivity derived from labeled 2,3,7,8-TCDD to liver proteins was observed in several studies. However, covalent binding to hepatic DNA was four times less than the levels of binding with other carcinogens (Poland and Glover 1979). This indicates that the typical mutation mechanism model (covalent binding/DNA alteration) may not be applicable in the case of CDDs. In addition, there is an evidence that 2,3,7,8-TCDD acts as a tumor promoter (Hebert et al. 1990; Poland et al. 1982), which is consistent with the increases in multiple-site tumors observed in exposed humans and animals.

2,3,7,8-TCDD is an atypical chemical because of its accumulation and long persistence in the body. Several studies demonstrated that 2,3,7,8-TCDD affects the adrenals, thymus (DiBartolomeis et al. 1987; Gorski et al. 1988b; Greenlee et al. 1985; Hochstein et al. 1988), and thyroid (Henry and Gasiewicz 1987; Hermansky et al. 1988; Hong et al. 1987; Lu et al. 1986; Rozman et al. 1985) and also alters the estradiol (Umbreit et al. 1987), testosterone, and dihydrotestosterone (Mebus et al. 1987; Moore et al. 1985) levels in the organism. A study with intact and ovariectomized rats indicated that ovarian estrogens are involved in 2,3,7,8-TCDD induced hepatocarcinogenesis (Lucier et al. 1991). Assuming that there is a relationship

between the 2,3,7,8-TCDD Ah receptor protein function and the steroid and thyroid receptor protein functions, 2,3,7,8-TCDD would interact with various hormone receptors (Holder and Menzel 1989). It has been proposed that 2,3,7,8-TCDD is a hormonal carcinogen causing effects in targeted organs and in secondary targets through hormonal imbalance. Furthermore, 2,3,7,8-TCDD may also promote the metabolism of procarcinogens to active intermediates by the induction of metabolizing enzymes as demonstrated *in vitro* in cultured human lymphocytes (Jaiswal et al. 1985; Kouri et al. 1974, 1978). The induction of these enzymes appears to be the subject of genetic polymorphism such that individuals who are highly inducible may be at high risk for the development of tumors.

Taken together, the results of the epidemiology studies and the animal studies suggest that 2,3,7,8-TCDD may be a human carcinogen. This is consistent with conclusions of several regulatory agencies. NTP (1998) considers 2,3,7,8-TCDD to be a substance that may reasonably be anticipated to be a carcinogen (limited evidence in humans, sufficient evidence in animals); NTP is currently considering a reclassification of 2,3,7,8-TCDD and the decision is pending. IARC (1997) has recently classified 2,3,7,8-TCDD in Group 1 based on limited evidence of carcinogenicity in humans and sufficient evidence in animals. EPA had classified 2,3,7,8-TCDD as a Group B2 carcinogen when considered alone and a Group B1 carcinogen when considered in association with phenoxyherbicides and/or chlorophenols (EPA 1985d, 1989d, 1991a). The Group B2 classification indicates that although evidence in humans is inadequate, the evidence in animals is sufficient to consider 2,3,7,8-TCDD a probable human carcinogen. The Group B1 classification indicates that there are not only sufficient animal data but also limited human data to support the consideration that 2,3,7,8-TCDD, in association with phenoxyherbicides and/or chlorophenols, is a probable human carcinogen. Moreover, in a proposed rule to add "Dioxin and Dioxin-Like Compounds" to the list of chemicals subject to release reporting requirements, EPA reiterated that, "Based on the EPA weight of evidence classification criteria, there is sufficient evidence to conclude that 2,3,7,8-TCDD is a probable human carcinogen" (EPA 1997c).

2.6 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 due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal 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 and 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 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 the newborn who has a low glomerular filtration rate and has 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 lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per

kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

There is a limited amount of information available on the toxicity of CDDs in children. Most of the available data come from a series of studies on children living in Seveso during the accidental release of airborne trichlorophenol contaminated with 2,3,7,8-TCDD. Shortly after the accident, early irritative dermal lesions (this effect may not have been related to 2,3,7,8-TCDD exposure) and chloracne were observed in a number of children. Erythema and edema, the main clinical features of the early irritative lesions, were only observed in children and young adults (less than 20 years old) (Caputo et al. 1988). Chloracne was observed in 187 individuals, 88% of them were children aged 0 to 14 years (Bisanti et al. 1980). Based on serum 2,3,7,8-TCDD levels measured in 30 Seveso residents with and without chloracne, Mocarelli et al. (1991) suggested that children may develop chloracne at lower 2,3,7,8-TCDD body burdens than adults following acute exposure to 2,3,7,8-TCDD. Other effects observed in the exposed children include a significant increase in the number of children with chloracne having clinical and electrophysiological signs of peripheral nervous system involvement (assessed 6 years after the accident) (Barbieri et al. 1988) and slight transient increases in serum γ-glutamyltransferase and alanine aminotransferase levels in boys aged 6-10 years (Mocarelli et al. 1986). Although the serum enzyme levels were higher than in non-exposed children, the values were within the normal range and were elevated 1, 2, and 3 years after the accident, but not after 4 or 5 years. Increased risks of Hodgkin's lymphoma, myeloid leukemia, and thyroid cancer were also reported among children who were 0–19 years old at the time of the Seveso accident (Pesatori et al. 1993). However, the differences in relative risks (RRs) for these cancer types between the Seveso residents and the control population did not reach statistical significance. Similar results were found in a 15-year follow-up study of this cohort (Bertazzi et al. 1997).

A wide variety of effects have been observed in adults exposed to 2,3,7,8-TCDD at work or following an accidental release of 2,3,7,8-TCDD into the environment. The primary targets appear to be the skin, liver, thyroid, and cardiovascular, endocrine, and immune systems; an increased cancer risk has also been observed. In the absence of data to the contrary, it is likely that these organs/systems will also be sensitive targets in children.

A number of human studies have investigated the potential of 2,3,7,8-TCDD to induce developmental effects. No significant increases in the incidence of birth defects have been observed in the children of parents living in Seveso at the time of the accident or during the next 6-year period (Bisanti et al. 1980;

Mastroiacovo et al. 1988) or in the children of men involved in the manufacture of chlorophenols (Townsend et al. 1982). In contrast, other studies have found increases in specific types of defects, although the total number of defects was not significantly altered. It is difficult to interpret these data because there is little consistency regarding the type of defect or the target organ/system. For example, a significant association between nervous system defects and paternal serum 2,3,7,8-TCDD levels was observed in the Ranch Hand cohort (Wolfe et al. 1995) and facial clefts were observed in Arkansas residents exposed to sprayed 2,4,5-T. The lack of exposure data, small sample sizes, and the lack of reliable data for birth defect rates prior to 2,3,7,8-TCDD exposure limits the power of the human studies to determine if an association between 2,3,7,8-TCDD exposure and developmental toxicity exists in humans.

The toxicity of 2,3,7,8-TCDD has been extensively examined in animal oral toxicity studies, and effects have been observed in most organs/systems. The animal studies clearly demonstrate that the developing organism is very sensitive to the toxicity of 2,3,7,8-TCDD. The types of effects observed in the offspring of animals exposed to 2,3,7,8-TCDD include fetal/newborn mortality, decreased growth, structural malformations, kidney anomalies, immunotoxicity, thymic atrophy impaired development of the reproductive system, and neurodevelopmental effects. The LOAELs for developmental effects are among the lowest identified in animals, and the chronic oral MRL is based on a developmental effect. The most sensitive developmental effects are impaired development of the reproductive system and neurobehavioral effects. *In utero* exposure to 2,3,7,8-TCDD adversely affects the development of the reproductive system in male and female offspring; studies have shown alterations in androgen levels, secondary sex organs, spermatogenesis, fertility, and sexual behaviors (Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Chaffin et al. 1996, 1997; Flaws et al. 1997; Gray and Ostby 1995; Gray et al. 1995, 1997a, 1997b; Heimler et al. 1998; Mably et al. 1992a, 1992b, 1992c). Gray and Ostby (1995) found decreased fertility in the female offspring exposed on Gd 8; no effects on fertility have been observed in female offspring exposed on Gd 15 (Gray et al. 1997a) or in male offspring (Gray et al. 1995; Mably et al. 1992c). Schantz and Bowman (Bowman et al. 1989b; Schantz et al. 1986, 1992; Schantz and Bowman 1989) found neurobehavioral alterations in the offspring of monkeys chronically exposed to dietary 2,3,7,8-TCDD (7 months prior to mating and during mating and lactation). Altered peer group behavior, cognitive deficits, and prolonged maternal care were observed. There are some data to suggest that other CDDs (2,7-DCDD, 1,2,3,7,8-PCDD, OCDD, and HxCDD) are also toxic to the developing organism (Madse and Larsen 1989; Schwetz et al. 1973). The observed developmental effects appear to be similar to those observed following *in utero* exposure to 2,3,7,8-TCDD. More details about these studies can be found in Sections 2.2.2.6, Developmental Effects, and 2.4.2, Mechanisms of Toxicity.

There is a limited amount of data on the toxicokinetic properties of CDDs in children or immature animals. A toxicokinetic model was constructed that accurately predicted the lifetime concentrations of 2,3,7,8-TCDD in adipose tissue, blood, liver, and feces at different ages (Kreuzer et al. 1997). In formula-fed infants, the model predicted that 2,3,7,8-TCDD lipid levels would decrease during the first year and subsequently increase, reaching a maximum at 16 years of age. In contrast, the model predicted an initial increase in 2,3,7,8-TCDD lipid levels in exclusively breast-fed infants followed by a 3-year decrease after weaning and merging at about 7 years with concentrations in formula-fed individuals. The half-life of nonmetabolic elimination (unchanged 2,3,7,8-TCDD) was calculated to be 0.42 years in newborns and 9.5 years in 40-year-old adults. The half-life of the fraction metabolized by the liver ranged from 1.5 years for newborns to approximately 10 years for a 40-year-old individual. The three times greater elimination half-life for the metabolized fraction relative to the nonmetabolized fraction in infants suggests that metabolic elimination does not play a major role in the elimination of 2,3,7,8-TCDD in infants. 2,3,7,8-TCDD accumulates preferentially in liver and adipose tissue. Accumulation in the liver is due to sequestration by the microsomal binding protein, CYP1A2. To the extent that this protein is developmentally regulated (Leeder and Kerns 1997), infants (<4 months old) might accumulate relatively less 2,3,7,8-TCDD in their livers than adults. Little is known about the metabolism of 2,3,7,8-TCDD in humans and it is unknown whether the metabolism of 2,3,7,8-TCDD or other CDDs differs between adults and children. In animals, phase II enzymes play an important role in the biotransformation and elimination of 2,3,7,8-TCDD. If this were the case in humans, it would be expected that very young infants would metabolize and eliminate 2,3,7,8-TCDD slower than adults since glucuronosyltransferase activity achieves adult levels by 6–18 months of age (Leeder and Kearns 1997).

CDDs are transferred from mother to offspring through the placenta and breast milk. Although there are human data indicating placental transfer of 2,3,7,8-TCDD (Kreuzer et al. 1997; Schecter et al. 1996b), quantitative data are not available. A study in mice administered a single dose of 2,3,7,8-TCDD on Gd 12 showed that the rate of accumulation of 2,3,7,8-TCDD in placental tissue reached a maximum in about 3 hours (Abbott et al. 1996); after 24 hours, 0.27% of the maternal dose was detected in the placenta. This issue is discussed in more detail in Section 2.3.4.4, Transfer of CDDs Through the Placenta and Breast Milk.

CDDs are lipophilic compounds that can concentrate in maternal milk and be transferred to the nursing infant. Numerous studies have examined the transfer of 2,3,7,8-TCDD and related chemicals to infants via breast milk and for the most part, the results showed that infants may absorb up to 95% of the administered

dose (Abraham et al. 1994, 1996; Dahl et al. 1995; McLachlan 1993; Pluim et al. 1993b). This percentage is similar to the percent of 2,3,7,8-TCDD absorbed (>87%) by an adult volunteer after ingestion of a single oral dose of 2,3,7,8-TCDD (Poiger and Schlatter 1986). As stated previously, it has also been shown that breast-fed infants have a larger 2,3,7,8-TCDD burden during the first year of life compared to formula-fed infants (Kreuzer et al. 1997). However, this initial higher burden does not translate into a higher lifetime burden. A number of human studies have examined breast-fed infants of mothers with high background levels of CDDs. These studies have found alterations in some markers of liver, thyroid, and immune function and neurodevelopment (neurological optimality score) (Huisman et al. 1995a; Koopman-Esseboom et al. 1994; Pluim et al. 1993b, 1994a; Weisglas-Kuperus et al. 1995); however, all of the markers were within the normal range. The impaired neurological optimality score that was observed in newborns was not significantly altered in children aged 6, 18, or 31 months (Ilsen et al. 1996; Huisman et al. 1995b; Pluim et al. 1996).

Subsequent sections of this chapter (Sections 2.7, 2.8, and 2.10) discuss the available information on biomarkers, interactions, and methods for reducing toxic effects. Most of the available information is from adults and mature animals; no child-specific information was identified, with the possible exception of biomarker data. However, there are some data to suggest that interactions with PCBs and CDFs may influence the developmental toxicity of 2,3,7,8-TCDD. Data from children living in Seveso suggest that serum 2,3,7,8-TCDD levels are reflective of exposure levels and are a sensitive indicator of past exposure. Likewise, it is likely that the available information in adults on interactions and methods for reducing toxic effects will also be applicable to children.

As discussed previously, children appear to be unusually susceptible to the dermal toxicity of 2,3,7,8-TCDD. The data are inadequate to assess whether they will also be more sensitive to other CDD effects. Additionally, the available animal data suggest that the developing fetus is very sensitive to 2,3,7,8-TCDD-induced toxicity. 2,3,7,8-TCDD appears to interfere with the development of the reproductive, immune, and nervous systems; the mechanisms of action for these toxic effects have not been elucidated.

2.7 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 (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to CDDs are discussed in Section 2.7.1.

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 CDDs are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to CDDs

Methods for measuring CDDs in biological fluids and tissues are available. Adipose tissue and liver are the primary storage site for CDDs and tissue samples have been analyzed in several studies. It was demonstrated that the relative (lipid-based) levels of 2,3,7,8-TCDD are similar in hepatic and adipose tissues (Leung et al. 1990a) and between adipose tissue and serum (Patterson et al. 1988; Schecter et al. 1990) from the same patients. However, this was not the case for more highly chlorinated dioxins; for example, for OCDD there is a 2:1 ratio between serum and adipose tissue lipid fractions (Schecter et al. 1990) and a 12:1 ratio between liver and adipose tissue levels (Thoma et al. 1990). However, the important TEQ variable was close to 1:1 ratio.

In the general population, adipose tissue levels of 2,3,7,8-TCDD ranged from non-detectable to 20.2 ppt in 128 Kansas City, St. Louis, and Springfield, Missouri, residents with no known special exposure to CDDs (Andrews et al. 1989). Similarly, 2,3,7,8-TCDD levels in adipose tissues were between 5 and 10 ppt in a sample of the general population in Canada, while OCDD levels ranged from 600 to 800 ppt in the cohort (Ryan et al. 1985a). Increased environmental exposure to CDDs was reflected by increased levels in adipose tissues. Residents of two California households who had eaten dioxin-contaminated beef and eggs had significantly elevated serum levels of 2,3,7,8-TCDD, PCDD, and HxCDD, compared with rural Californians who did not eat contaminated beef and eggs (Goldman et al. 1989). 2,3,7,8-TCDD serum lipid levels ranged from 2.8 to 750 ppt in individuals with possible recreational, residential, or occupational exposure in Missouri (Patterson et al. 1986a). Several other studies reported increased concentrations of 2,3,7,8-TCDD in adipose tissues (Beck et al. 1989c; Fingerhut et al. 1989; Patterson et al. 1989b) or serum lipid (Fingerhut et al. 1989; Patterson et al. 1989b) of occupationally exposed workers. The highest 2,3,7,8-TCDD levels reported ranged between 42 and 750 ppt in adipose tissue lipid and between 61 and 1,090 ppt in the serum lipid of Missouri chemical workers (Patterson et al. 1989b). Based on a mean of 208 ppt 2,3,7,8-TCDD in the serum lipid of chemical workers measured at least 17 years postexposure, and a mean biological half-life level of 7 years, it was estimated that the serum lipid level shortly after exposure would have been approximately 2,313 ppt (range, 6.4–14,673) (Fingerhut et al. 1989). The major disadvantage of these studies is a lack of information regarding actual 2,3,7,8-TCDD exposure. Studies in a population exposed to 2,3,7,8-TCDD in the Seveso industrial accident found serum lipid

2,3,7,8-TCDD levels in exposed individuals as high as 56,000 ppt in the highly contaminated zone where soil samples ranged from 956 to 1,185 µg 2,3,7,8-TCDD/m^2 (Mocarelli et al. 1991); these serum samples were collected about a month after exposure and were recently analyzed. Chloracne did not always develop in the individuals with highly elevated serum 2,3,7,8-TCDD levels, although it did occur in all who had levels above 12,000 ppt. In the most recent National Human Adipose Tissue Survey (NHATS), conducted in fiscal year 1987, it was found that the average concentration of 2,3,7,8-TCDD in the adipose tissue of the U.S. population was 5.38 ppt, increasing from 1.98 ppt in children under 14 years of age to 9.4 ppt in adults over 45 (Orban et al. 1994). The average concentration of 2,3,7,8-TCDD was found to increase at an average rate of 0.83 ppt per decade for individuals under age 31, and at an average rate of 1.52 ppt per decade for the older population. The study also found no statistical evidence of differences in the average levels for populations representing different sexes and racial groups nationwide. Furthermore, a comparison of mean concentrations of 2,3,7,8-TCDD and OCDD between the 1982 and 1987 NHATS revealed no statistically significant differences between the two surveys. For OCDD the values were 768 and 724 ppt in the 1982 and 1987 surveys, respectively (Orban et al. 1994).

Similarly, no exact exposure data were available in Vietnam veteran studies. In general, tissue samples for analyses were taken several (approximately 10–20) years after exposure, which represents another limitation of these studies. Increased adipose 2,3,7,8-TCDD levels (up to 99 ppt) were recorded in Vietnam War veterans involved in Operation Ranch Hand (Gross et al. 1984; Schecter et al. 1989a). In a small group of potentially exposed Vietnam veterans, adipose tissue 2,3,7,8-TCDD levels ranged from non-detectable to 11 ppt with a mean of 5.8 ppt (Schecter et al. 1989a). Schecter et al. (1989a) noted that the veterans with adipose tissue levels of $8 ppt were considered to have slightly elevated values or values within the normal range. In another study of 646 ground troop veterans, only two individuals had serum 2,3,7,8-TCDD levels above 20 ppt in the lipid fraction (CDC 1988). In the rest of the cohort, the median 2,3,7,8-TCDD levels ranged from 3.2 to 4.3 ppt and did not differ significantly from the levels found in the control group of non-Vietnam veterans (CDC 1988; MMWR 1987). It was concluded that those who did not handle or spray herbicides were not highly exposed to 2,3,7,8-TCDD (CDC 1988). With regard to the long time period between exposure and serum analysis, the authors argued that, assuming first-order kinetics and 2,3,7,8-TCDD's half-life of 7 years in humans, the study had enough statistical power to detect differences between the exposed and control groups (CDC 1988). Elevated CDD levels were also measured in some patients treated in a hospital in South Vietnam (Phiet 1989; Phuong et al. 1989b). However, these reports involved too few patients to give any conclusive results. In a more recent expanded half-life study of 337 Vietnam veterans, a median observed half-life of 11.5 years was calculated for

2,3,7,8-TCDD (Wolfe et al. 1994). The nonparametric 95% CI was 10–14.1 years. A review of CDD levels in human tissues from various populations can be found in Schecter et al. (1994c).

CDDs have also been detected in breast milk of women exposed to high levels of CDDs and in women presumably exposed to background levels. High 2,3,7,8-TCDD levels (mean of 484 pg/g milk fat; 18 pg/g whole milk) were found in the milk of mothers from South Vietnam in 1970; the levels dropped to a mean of 12 pg/g milk fat (0.47 pg/g milk) by 1985 (Schecter et al. 1987a) and 7.5 pg/g milk fat in samples collected between 1984 and 1992 (Schecter et al. 1995). Mean 2,3,7,8-TCDD levels in breast milk samples (collected in 1984) in mothers from South Vietnam, North Vietnam, and the United States were 0.68, not detectable, and 0.19 pg/g whole milk (Schecter and Gasiewicz 1987b). The total CDD and CDF levels (expressed as TEQs) in these samples were 1.11, 0.065, and 1.04 pg/g milk. Results from the analysis of 526 individual milk samples from the German general population revealed a mean 2,3,7,8-TCDD concentration of 3.2 pg/g milk fat (Fürst et al. 1994). The analysis also showed the presence of only 2,3,7,8-chlorine-substituted congeners. OCDD was the most concentrated congener with a mean level of 208 pg/g milk fat. In general, the levels in milk decreased with decreasing degree of chlorination from octa- to tetra-CDD. The total TEQs, including CDFs, was 29.3 pg/g milk fat. Fürst et al. (1994) estimated that the average daily intake of 2,3,7,8-TCDD via human milk for an infant weighing 5 kg is 15.4 pg/kg/day, and the mean total dioxin equivalents amounted to 140.6 pg/kg/day. Both parity and the length of time the woman has been lactating influence the CDD concentration in breast milk.

A reverse transcriptase polymerase chain reaction (RT-PCR) method was developed to quantitate CYP1A1 mRNA levels on total RNA extracts from mitogen-stimulated human blood lymphocytes cultured in the presence or absence of 10 nM 2,3,7,8-TCDD (Van den Heuvel et al. 1993). Although CYP1A1 gene expression can be monitored by measuring EROD activity (CYP1A1) or mRNA expression (using conventional RNA hybridization), RT-PCR is a much more sensitive approach. The average CYP1A1 mRNA levels in the cultured, 2,3,7,8-TCDD-treated cells was approximately 21 times higher than that in the non-2,3,7,8-TCDD-treated cells. In uncultured, nonstimulated lymphocytes from volunteers, CYP1A1 mRNA could be reproducibly measured at levels that were 10–40-fold lower than in mitogen-stimulated lymphocytes. In comparison, EROD activity measured in uncultured, nonstimulated lymphocytes was indistinguishable from measurements on reagents controls, which proved the high sensitivity of the RT-PCR approach. In a group of 6 smokers, the average level of CYP1A1 message was approximately 2 times higher than in a group of 6 nonsmokers, although there was great variability in the group of smokers. Based on these preliminary results, Van den Heuvel et al. (1993) suggested that CYP1A1 gene expression

in peripheral blood lymphocytes may be used as a human exposure marker for 2,3,7,8-TCDD and related compounds.

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

2.7.2 Biomarkers Used to Characterize Effects Caused by CDDs

Chloracne is one effect that is clearly associated with exposure to high levels of CDDs and other halogenated organic chemicals, and has been observed in some individuals who were exposed occupationally or in the environment to increased levels of 2,3,7,8-TCDD or chemicals contaminated with 2,3,7,8-TCDD. However, while the presence of chloracne indicates exposure to CDDs or other halogenated organic compounds, its absence does not preclude such exposure. For example, in a cohort from the Seveso incident, no chloracne was observed below an initial serum lipid 2,3,7,8-TCDD level of 800 ppt (body burden of 2.5 µg/kg, assuming 22% body fat and 70 kg body weight); above 12,000 ppt (body burden of 38 µg/kg) chloracne was always observed; and between 800 and 12,000 ppt the occurrence of chloracne was sporadic (Mocarelli et al. 1991). In the Yu-Cheng population, chloracne was associated with a body burden in 2,3,7,8-TCDD equivalents of 2–3 µg/kg body weight, or about 140–210 µg for a 70-kg adult (Ryan et al. 1990).

Biochemical changes (raised serum hepatic enzyme levels, disorders of lipid and carbohydrate metabolism, unbalanced porphyrin metabolism) and/or an enlarged liver can indicate effects induced by 2,3,7,8-TCDD exposure, but these effects are not specific for this or other compounds. Light and electron microscope changes in the liver (e.g., lipid droplets in parenchymal cells, increased endoplasmic reticulum, enlarged and pleomorphic mitochondria) are also sensitive but nonspecific biomarkers for exposure to CDDs (Schecter et al. 1985b). When biochemical changes in the placenta of women exposed in the Yu-Cheng incident were evaluated for use as possible biomarkers, the EGF receptor autophosphorylation effect was found to be associated with decreased birth weight in the neonates (Lucier et al. 1986). The authors suggested using this response as a biomarker of effect for all toxic chlorinated aromatic compounds.

2.8 INTERACTIONS WITH OTHER CHEMICALS

Several studies were located regarding interactions that affect the toxicity of CDDs. Probably the most important interactions that have an impact on human health are those involving CDDs, CDFs, and PCBs. It has been recognized that chloroaromatics cause a complex of similar effects that vary in severity depending on the number of chlorine atoms, positional substitution, and species susceptibility. Sufficient information is available for assessment of risk associated with exposure to 2,3,7,8-TCDD. However, exposure to a mixture of chloroaromatics is common in the general environment. The assessment of health risk resulting from exposure to chemical mixtures of chloroaromatics was enabled by the development of TEFs (2,3,7,8-TCDD equivalence factors) that relate the relative toxic potency for CDDs and CDFs to that of 2,3,7,8-TCDD (EPA 1989). It was assumed based on previous literature data (Eadon et al. 1986) and in animal dosing studies (Van den Berg et al. 1989), that CDDs and CDFs have an additive effect in the organism when weighted for relative toxicity compared to 2,3,7,8-TCDD (for further information see Sections 2.4 and 2.5). The assumption of additivity was later supported by experimental data. The concept of TEFs was used, for example, to assess the potential toxicity of background levels of CDFs and CDDs in general populations based on body burdens of indicator CDDs that were associated with chloracne and other effects in the Yusho and Yu-Cheng rice oil poisoning incidents (Ryan et al. 1990).

However, some recent studies further investigated the interactions of various chloroaromatics and indicated that the interactions may be more complicated. *In vitro* studies compared relative toxicity of various chloroaromatics in human cell lines monitoring enzyme induction and binding to the Ah receptor that mediates the induced responses (Nagayama et al. 1985; Safe 1987). *In vivo* studies concentrated on monitoring of enzyme induction, inhibition of body weight gain and immunotoxic and teratogenic effects. Coexposure of Long Evans rats to 6-methyl-1,3,8-trichlorodibenzofuran (MCDF) and 2,3,7,8-TCDD induced a partial inhibition of the monooxygenase enzyme-induction response caused by 2,3,7,8-TCDD treatment alone (Harris et al. 1989b). Although MCDF did not decrease the levels of occupied nuclear 2,3,7,8-TCDD Ah receptors, it inhibited the effects of 2,3,7,8-TCDD on the cytosolic Ah receptor (Harris et al. 1989b).

Other studies further indicated that PCBs may antagonize Ah receptor-mediated responses to 2,3,7,8-TCDD. In a recent review, Van den Berg et al. (1994) suggested that toxicokinetic factors contribute to the observed nonadditive toxicological and biological effects. Co-treatment of C57BL/6 mice with various commercial Aroclors (PCB mixtures) and 2,3,7,8-TCDD resulted in antagonizing the

2,3,7,8-TCDD-mediated inhibition of the splenic plaque-forming cell response (Bannister et al. 1987; Davis and Safe 1989). Similarly, significant antagonism of 2,3,7,8-TCDD and Aroclor 1254 was observed in the induction of cytochrome P-450-dependent monooxygenases in C57BL/6J mice (Bannister et al. 1987). The effects were dependent on the dose of both 2,3,7,8-TCDD and Aroclor 1254 and on their respective ratios. The ratios of Aroclor 1254/2,3,7,8-TCDD that induced antagonist reactions were comparable to the ratios of PCBs/CDDs found in human tissues and environmental samples. The authors speculated that less-toxic chlorinated compounds may have a protective effect against the more-toxic compounds in the environment. However, by comparing the immune sensitivities of both Ah responsive and Ah less-responsive mouse strains, it was demonstrated that a complex mixture of contaminants taken from the Love Canal site was immunosuppressive and that this effect was primarily due to the 2,3,7,8-TCDD component of the mixture, although 2,3,7,8-TCDD was a very minor component, and there was little interaction with the other hydrocarbon components of the mixture (Silkworth et al. 1989a).

Experimental studies have shown that interactions of 2,3,7,8-TCDD and CDFs or PCBs resulted in fetotoxic and teratogenic effects in the offspring of exposed animals. Exposure of pregnant mice to 2,3,7,8-TCDF resulted in cleft palates and hydronephrosis in the offspring (Hassoun et al. 1984). The results obtained in different strains of mice indicated an association with the Ah locus. Comparable results were obtained previously in mice exposed to 2,3,7,8-TCDD (Abbott and Birnbaum 1989a; Abbott et al. 1987a, 1987b; Courtney 1976). When C57BL/6N mice were treated orally with 2,3,7,8-TCDD and 2,3,7,8-TCDF on gestational day (Gd) 10, hydronephrosis and cleft palates were observed in the offspring (Weber et al. 1985). The effects of both chemicals were additive. Similarly, an increased incidence (10-fold) of cleft palates was observed in offspring of C57BL/6N mice after a combined treatment with 2,3,7,8-TCDD and 2,3,4,5,3',4'-hexachlorobiphenyl during gestation, as compared with those treated with 2,3,7,8-TCDD alone (cleft palate was not observed when 2,3,4,5,3',4'-hexachlorobiphenyl was administered alone) (Birnbaum et al. 1985). In contrast, no potentiation of CDD-mediated effect was found with 2,4,5,2',4',5'-hexachlorobiphenyl. Furthermore, co-treatment of pregnant C57BL/6J mice with Aroclor 1254 and 2,3,7,8-TCDD resulted in a sharp decrease in the incidence of cleft palate per litter (8.2%) compared with those treated with 2,3,7,8-TCDD alone (62%) (Haake et al. 1987).

Similarly, 2,3,7,8-TCDD-induced fetotoxicity and teratogenicity were altered by co-exposure to other chemicals. A synergistic effect on the induction of cleft palates was observed in offspring of C57BL/6N mice treated orally with 2,3,7,8-TCDD and retinoic acid on Gd 10 or 12 (Abbott and Birnbaum 1989b; Birnbaum et al. 1989b). However, the co-administration of retinoic acid did not influence the incidence of

2,3,7,8-TCDD-induced hydronephrosis, nor did 2,3,7,8-TCDD affect the incidence or severity of limb-bud defects induced by retinoic acid (Birnbaum et al. 1989b). A synergistic effect was observed when 2,3,7,8-TCDD (orally) and hydrocortisone (subcutaneously) were administered to C57BL/6N mice on Gd 10–13 (Birnbaum et al. 1986). The incidence of cleft palate in the offspring increased to 100% following the combined treatment. Pretreatment of pregnant NMRI mice with benzo(*a*)pyrene subcutaneously 5 hours prior to an intraperitoneal injection of 2,3,7,8-TCDD caused an increase in CDD-induced lethality but did not alter the rate of cleft palate formation (Hassoun 1987). Offspring of male mice, treated with chlorinated phenoxy acids and 2,3,7,8-TCDD in their feed for 8 weeks before the mating, did not differ in their development or survival from offspring in the control group (Lamb and Moore 1981).

Results in B6C3F_1 mice indicated that α-naphthoflavone antagonizes 2,3,7,8-TCDD in induction of splenocyte EROD activity (Blank et al. 1987). It was further suggested that α-naphthoflavone impedes 2,3,7,8-TCDD suppression of B lymphocyte differentiation by competing for binding to the Ah receptor. The mechanism of interaction of these chemicals was studied *in vitro* using rat hepatic cytosol or mouse hepatoma cells (Gasiewicz and Rucci 1991). The results indicated that α-naphthoflavone acts as a 2,3,7,8-TCDD antagonist by binding to the Ah receptor and forcing on it a conformation that cannot identify the DNA recognition sequence contained in the dioxin-responsive enhancer element of the CYP1A1 gene. In contrast, *in vitro* experiments showed that co-exposure of a thymus organ culture with the weakly toxic β-naphthoflavone and 2,3,7,8-TCDD results in a significant increase in the lymphoid inhibitory effect mediated by 2,3,7,8-TCDD (Hassoun 1987).

Hexachlorobenzene acted like a weak Ah receptor agonist and caused an up to 40% decrease in specific hepatic cytosol binding of 2,3,7,8-TCDD in rat cells (Hahn et al. 1989b). Similarly, 2,3,7,8-TCDD-induced myelotoxicity and enzyme induction was antagonized by 1-amino-3,7,8-trichlorodibenzo-p-dioxin in B6C3F_1 mice presumably by competitive binding to the cytosolic Ah receptor (Luster et al. 1986). Comparable effects were observed *in vitro* in murine bone-marrow-cells cultures. Treatment of Fischer 344 rats orally with di(2-ethylhexyl)phthalate (DEHP) before or after oral administration of 2,3,7,8-TCDD reduced the hyperlipidemia induced by the latter compound (Tomaszewski et al. 1988). Furthermore, DEHP pretreatment followed by daily doses of this hypolipidemic substance was partially protective against 2,3,7,8-TCDD-induced mortality, wasting, and liver fatty changes.

The addition of activated charcoal or dehydrocholic acid to the feed, protected animals (C57BL/6J mice, CD-COBS rats, and guinea pigs) from increased mortality caused by a single lethal dose of 2,3,7,8-TCDD (Manara et al. 1984). In the case of the former agent, the effect was probably due to the general high binding ability of superactivated charcoal; since no other antidote is known, its use for therapeutic purposes was recommended. Protective effects of ascorbic acid (administered orally) and butylated hydroxyanisole (BHA) (administered orally) against 2,3,7,8-TCDD given by gavage were investigated in Sprague-Dawley rats (Hassan et al. 1987). BHA administration partially protected rats from losses in organ weights and 2,3,7,8-TCDD-induced lipid peroxidation and inhibition of glutathione peroxidase activity. In contrast, ascorbic acid had no protective effects.

Data regarding interactions affecting the toxicity or toxicokinetics of other chemicals by 2,3,7,8-TCDD were limited. Dermal pretreatment with 2,3,7,8-TCDD inhibited the induction of skin tumors by subsequently applied benzo(*a*)pyrene or dimethylbenz(*a*)anthracene in Sencar mice (Cohen et al. 1979). It was proposed that 2,3,7,8-TCDD caused qualitative alteration of hydrogen binding to DNA. In addition, 2,3,7,8-TCDD may also promote the metabolism of procarcinogens (e.g., 3-methylcholanthrene) to active metabolites by the induction of metabolizing enzymes (Kouri et al. 1974, 1978).

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to CDDs than will most persons exposed to the same level of CDDs 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 may result in reduced detoxification or excretion of CDDs, or compromised function of target organs affected by CDDs. Populations who are at greater risk due to their unusually high exposure to CDDs are discussed in Section 5.6, Populations With Potentially High Exposure.

No data were located regarding unusually susceptible subpopulation in humans. Animal data showed developmental effects of 2,3,7,8-TCDD in fetuses and newborns exposed *in utero* and via breast-feeding, respectively (Abbott and Birnbaum 1989b; Giavini et al. 1982, 1983; Håkansson et al. 1987; Weber et al. 1985) (see Section 2.2.2.6). The experimental data suggest that the prenatal and postnatal population may be more sensitive to 2,3,7,8-TCDD-induced effects; however, the levels of exposure necessary to induce such effects are not known. Data in mice indicated that strain differences in sensitivity to 2,3,7,8-TCDD toxicity exist and are associated with the Ah receptor (Poland and Glover 1980). It has been shown that

the Ah receptor exists in human lymphoid tissue and that its concentration is variable between persons (Hayashi et al. 1994; Lorenzen and Okey 1991). As noted in Section 2.4, 2,3,7,8-TCDD may promote the metabolism of procarcinogens (e.g., contained in cigarette smoke) to active intermediates by the induction of metabolizing enzymes. The induction of these enzymes in humans appears to be subject to genetic polymorphism so that individuals who have an Ah receptor with high affinity for 2,3,7,8-TCDD and related chemicals may be at the highest risk for the development of lung tumors (Antilla et al. 1991; Bartsch et al. 1990; Kawajiri et al. 1990; McLemore et al. 1990; Uematsu et al. 1991).

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to CDDs. 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 CDDs. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No texts were found that provided specific information about treatment following exposures to CDDs.

2.10.1 Reducing Peak Absorption Following Exposure

No specific information was located regarding the reduction of peak absorption of CDDs by the oral and inhalation routes of exposure in humans. Weber et al. (1992d) examined the effect of four decontamination protocols on the residency time of 2,3,7,8-TCDD in intact or damaged human post-mortem skin *in vitro*. Damage was simulated by stripping of the stratum corneum. 2,3,7,8-TCDD was applied to the skin for 100 minutes and one of the following protocols was performed: the sample was wiped with dry, adsorbent material (cotton balls); a 10-minute topical treatment with mineral oil was followed by dry wiping with cotton balls; a 10-minute topical treatment with mineral oil was followed by wiping with acetone-soaked cotton balls; and the sample was washed with water and soap. In intact skin, mineral oil treatment and acetone wipes reduced by about two-fold the amount of 2,3,7,8-TCDD in the stratum corneum. Mineral oil plus dry wipes reduced the amount of 2,3,7,8-TCDD in the stratum corneum by about 33%, whereas dry wiping alone was ineffective. However, all protocols were equally effective in reducing the amount of 2,3,7,8-TCDD in the epidermis and upper dermis by factors of up to 10. In damaged skin, by dry wiping with adsorbent material 2,3,7,8-TCDD was rubbed into the skin, leading to increased concentrations in the

various layers of the skin. In contrast, mineral oil treatment followed either by dry wipes or by acetone wipes, and washing with water and soap decontaminated the damaged skin quite effectively. The authors (Weber et al. 1992d) noted that the effect of decontamination was most pronounced at a skin depth between 160 and 500 μm, which is the depth at which vascularization begins and, therefore, the protocols discussed should be particularly effective in reducing systemic absorption of 2,3,7,8-TCDD from the skin.

2.10.2 Reducing Body Burden

Limited information was located regarding reducing body burden following exposure to CDDs in humans. A recent study examined the influence of short-term dietary measures on CDD and CDF concentrations in human milk (Pluim et al. 1994c). The authors hypothesized that mobilization of fatty acids from adipose tissue cause the concomitant release of CDDs and CDFs, which will then be eliminated in the breast milk. Two diets were tested for their ability to reduce the concentration of CDDs and CDFs in human milk: a low-fat/high carbohydrate/low CDD and CDF diet (16 women), and a high-fat/low carbohydrate/low CDD and CDF diet (18 women). The authors also analyzed the fatty acid pattern of the milk to determine whether the dietary changes were sufficient to change the milk-fat composition. The test diets were followed for 5 consecutive days in the fourth week after delivery. Body weights were not affected by the experimental diets. The results showed that the fat content of the milk did not decrease in either group during the test diet. Furthermore, there was no significant change in CDD and CDF concentration in milk fat after treatment with the experimental diets. However, the percentage of medium-chain fatty acids (MCFA) changed significantly. In the low-fat/high carbohydrate diet group, the percentage of MCFA increased while the percentage of C_{18}:1ω9 fatty acids (fatty acid with 18 straight-chain carbon atoms, 1-methylene-interrupted double bond and 9 carbon atoms from the terminal methyl group to the nearest double bond) decreased. In the high-fat/low carbohydrate diet group the changes were in the opposite direction. According to the authors, the results would indicate that the concentration of CDDs and CDFs in milk fat may be independent of the source of the fatty acids. Alternatively, they indicate that the dieting period may have been too short or the dietary changes in fat and carbohydrate intake may have not been large enough.

Using a fugacity-based PBPK model to evaluate elimination of 2,3,7,8-TCDD from humans, assuming a background 2,3,7,8-TCDD intake of 50 pg/day, Kissel and Robarge (1988) estimated that daily consumption of 10 g of a nonabsorbable oil would reduce the steady-state adipose tissue concentration of 2,3,7,8-TCDD from 7.7 ppt to 3 ppt. At an adipose tissue level of 50 ppt, the apparent half-life of

2,3,7,8-TCDD would be decreased by consumption of the nonabsorbable oil from 5.2. to 2.1 years. However, this is a theoretical assumption based on the PBPK model.

Zober and Päpke (1993) reported that serum lipid 2,3,7,8-TCDD levels increased from 17 ppt to 32 ppt in a patient who lost >7 kg of weight in a 5-month period. The serum lipid concentrations of 1,2,3,6,7,8-HxCDD, 1,2,3,4,5,7,8-HpCDD, and OCDD also increased during this period. Fasting appeared to relieve signs and symptoms of intoxication in a group of patients who ingested rice oil contaminated with the structurally related PCBs and CDFs (Yu-Cheng incident) (Imamura and Tung 1984). The authors suggested that fasting may stimulate mobilization of the chemicals from adipose tissue to the liver where they are then metabolized, which would facilitate excretion and reduce body burden. However, the findings of that study should be interpreted with caution because a control group was not used, small number of subjects were evaluated, the patients volunteered for the study, and some of the end points that were evaluated were subjective. Promotion of fecal excretion of CDFs and PCBs by cholestyramine, a hypercholesterolemia therapeutic agent used in the treatment of poisoning by chlorinated organic agricultural chemicals, was inconclusive in a clinical trial with six Yusho patients (Iida et al. 1991; Murai et al. 1991).

In experimental animals, administration of a diet containing 2.5 or 5% activated charcoal substantially reduced mortality due to a single lethal oral dose of 2,3,7,8-TCDD in rats, mice, and guinea pigs (Manara et al. 1984). Also, feed with 0.25 or 0.5% cholic acid had a similar protective action in mice (Manara et al. 1984). The effect of activated charcoal was attributed to increased clearance of unabsorbed 2,3,7,8-TCDD from the body; the mechanism of protection by cholic acids was unclear.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

There are no established methods for interfering with the mechanism of action of CDDs. Many of the toxic effects of 2,3,7,8-TCDD and structurally related halogenated aromatic hydrocarbons have been shown to be mediated through the Ah receptor (see Section 2.4 for details). The sequence of events associated with the receptor-mediated mechanism involve entry of 2,3,7,8-TCDD into the cell, binding to the cytosolic Ah receptor, binding of the receptor-ligand complex to DNA recognition sites, and expression of specific genes and the translation of their protein products. Although speculative, it is possible that interference with this mechanism may lead to a more specific treatment for reducing some of the toxic effects of 2,3,7,8-TCDD and structurally related chemicals. Future research on Ah receptor antagonists may provide new insights

for clinical treatment of the Ah receptor-mediated toxicity of 2,3,7,8-TCDD and other Ah receptor agonists.

2.11 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 CDDs 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 CDDs.

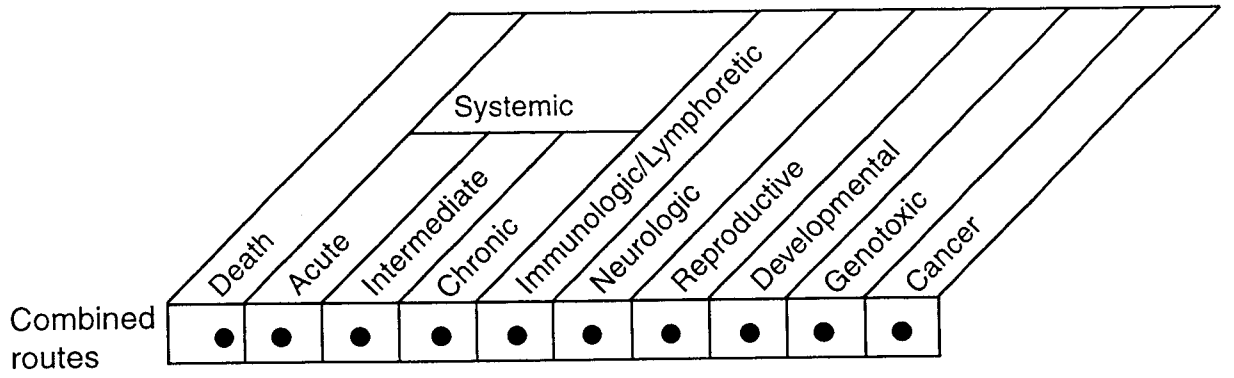
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

2.11.1 Existing Information on Health Effects of CDDs

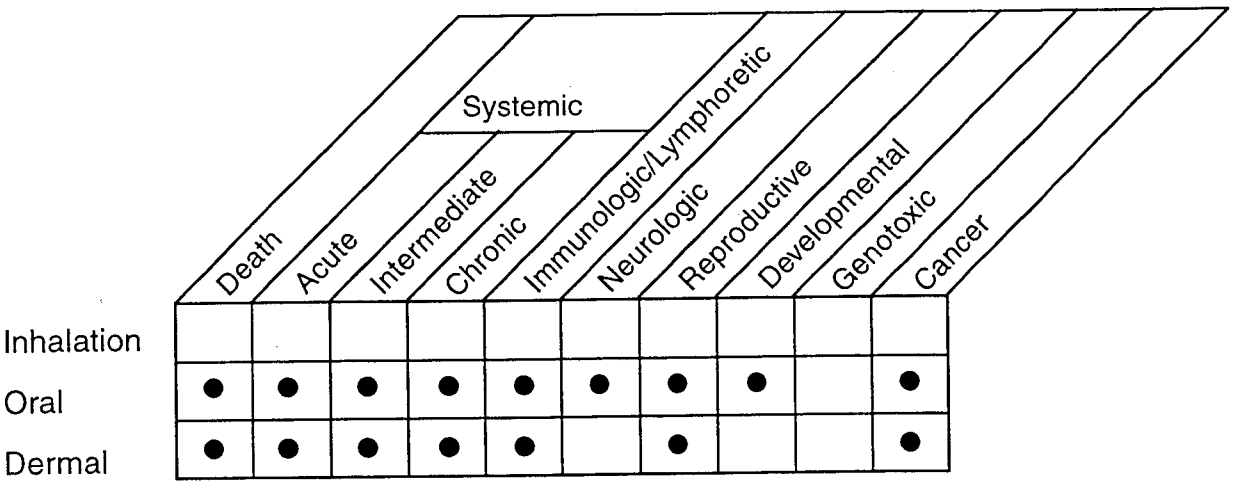
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to CDDs are summarized in Figures 2-5 and 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of CDDs. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figures 2-5 and 2-6, information is available regarding death, systemic, immunological, neurological, developmental, reproductive, and genotoxic effects and cancer in humans. Most of the available information is for 2,3,7,8-TCDD. Most of this information is negative or inconclusive except for

Figure 2-5. Existing Information of Health Effects of 2,3,7,8-TCDD



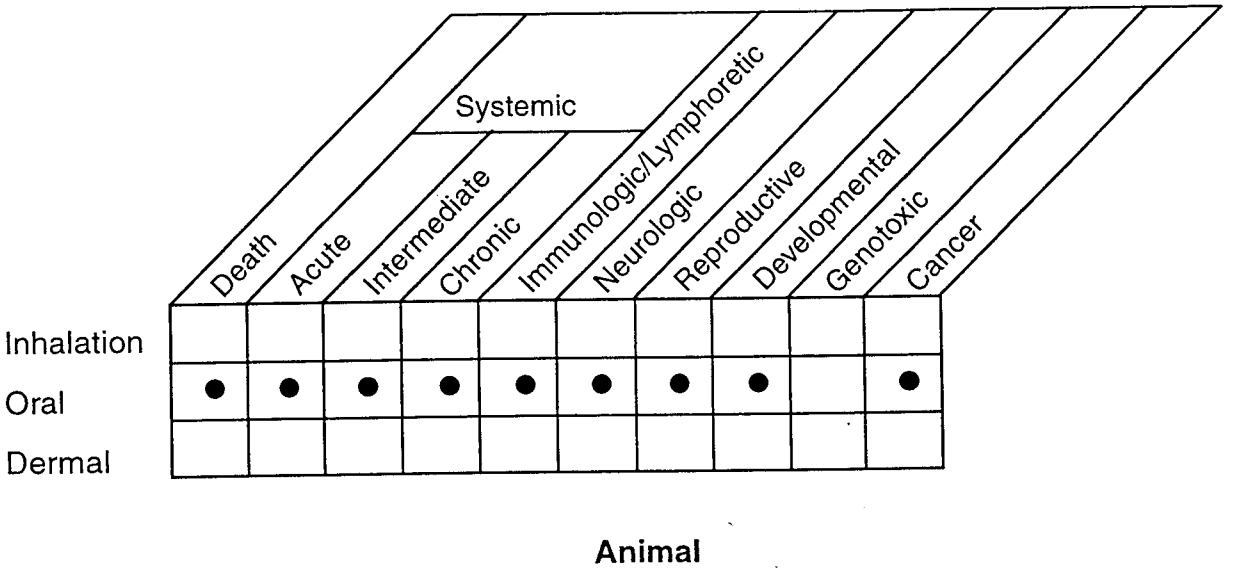
Human



Animal

● Existing Studies

Figure 2-6. Existing Information of Health Effects of Other CDDs



● Existing Studies

dermal effects and cancer. As previously mentioned, exposure to humans probably occurs by a combination of the inhalation, oral, and dermal routes. No information is available regarding effects of a single route of exposure in humans. However, food is the major source of human exposure in the general population; therefore, the oral route is the most significant exposure route.

Oral and dermal studies in animals provide data on death, systemic effects after acute-, intermediate-, and chronic-duration exposure, and immunological, reproductive, and cancer effects. Furthermore, data exist regarding neurological, developmental, and genotoxic effects after oral exposure. No data were located regarding effects in animals after inhalation exposure to CDDs.

2.11.2 Identification of Data Needs

As discussed in Section 2.5, the EPA and other agencies and scientists are using the TEF scheme as an alternative interim approach for hazard evaluation of CDDs and CDFs. Since toxicological data for other CDD congeners is more limited, additional congener-specific studies would provide valuable data for validating the TEF approach. *In vitro* and short-term parenteral injection studies using sensitive end points (i.e., enzyme induction, immune alterations) have been used for this purpose, but studies using other end points, the oral route, and/or longer durations of exposure would be more informative. Since the database for CDD effects not mediated through the Ah receptor is limited, additional studies may be relevant to understanding whether acute versus chronic responses to 2,3,7,8-TCDD occur by different mechanisms.

CDDs and the structurally related CDFs and dioxin-like PCBs are of concern to ATSDR because of the potential of these chemicals to harm health at relatively low doses. As discussed in Section 2.5, many of the toxic effects of these compounds appear to be mediated by a common mechanism, and CDDs frequently occur with CDFs in the environment. Therefore, due to the common mechanism of toxicity, total toxicity of a CDD/CDF mixture probably results from the added contribution (not necessarily linear) of both classes of chemicals. Because of this, the complex issue of appropriate methodology for quantitatively assessing health risks of CDDs and CDFs is currently being evaluated by ATSDR. Additional information on toxic interactions between CDDs and CDFs, as well as PCBs, would facilitate health risk assessment of this class of chemicals.

Acute-Duration Exposure Acute exposure of humans to 2,3,7,8-TCDD can cause chloracne and hepatic effects (Goldman 1973; Reggiani 1980). Specifying the route of exposure in these human cases is

difficult because the individuals were probably exposed by a combination of routes. Furthermore, human data did not provide any information regarding exposure levels and co-exposure to other chemicals confounds the results. Also, in most cases, the exposed subjects were examined long after exposure occurred. Acute oral exposure to 2,3,7,8-TCDD caused delayed type of death in all animal species tested, and LD_{50} values have been determined for rats (NTP 1982b; Schwetz et al. 1973; Walden and Schiller 1985), minks (Hochstein et al. 1988), rabbits (Schwetz et al. 1973), guinea pigs (McConnell et al. 1984; Schwetz et al. 1973), and hamsters (Henck et al. 1981). Furthermore, an acute LD_{50} was calculated for rats and mice exposed to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980). No deaths were observed with other congeners (2,7-DCDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,8,9-OCDD) (NTP 1982b) tested, and 2,3,7,8-TCDD proved to be the most toxic CDD. However, interspecies and interstrain differences were found in the susceptibility to CDDs. Systemic effects observed in animals after acute oral exposure to 2,3,7,8-TCDD included cardiovascular (Hochstein et al. 1988; McConnell et al. 1978b), gastrointestinal (Theobald et al. 1991), hematological (Christian et al. 1986), hepatic (Christian et al. 1986; Kelling et al. 1985; Walden and Schiller 1985), renal (Christian et al. 1986; McConnell et al. 1978b), endocrine (Bastomsky 1977; Bestervelt et al. 1993; Fan and Rozman 1995; Potter et al. 1986; Weber et al. 1995), dermal effects (Greig 1984; McConnell et al. 1978b), and body weight loss (Kelling et al. 1985; Moore et al. 1985; Seefeld and Peterson 1984; Weber et al. 1994, 1995). Hepatic and body weight effects were the main signs of 2,3,7,8-TCDD toxicity and occurred also after exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980). Furthermore, immunological effects were observed following low oral doses of 2,3,7,8-TCDD (Burleson et al. 1996; White et al. 1986), and an acute oral MRL was based on a NOAEL for immunological effects (Burleson et al. 1996). In addition, the dermal LD_{50} for 2,3,7,8-TCDD has been determined in rabbits (Schwetz et al. 1973). Since only dermal changes were investigated following acute dermal exposure (Puhvel et al. 1982), further studies could provide useful information regarding additional endpoints; dermal contact is a relevant route of exposure at waste sites where CDDs may be stored. Limited data were located regarding effects in animals after acute inhalation exposure to CDDs (Diliberto et al. 1996; Nessel et al. 1992). Further studies by the inhalation route of exposure would be useful since toxicokinetic data in rats suggest that this could be an important route for systemic absorption of CDDs (Diliberto et al. 1996).

No information was located regarding health effects of other congeners in humans, and limited data exist about effects caused by an acute exposure to these congeners in animals. The information would be useful for populations living near hazardous waste sites who may be exposed to CDDs for acute durations. Should a case of high acute exposure to 2,3,7,8-TCDD occur in humans, prompt comprehensive

examination of those exposed would provide greatly needed information. Furthermore, follow-up medical surveillance of such a population should be conducted for as long as possible.

Intermediate-Duration Exposure. Intermediate-duration exposure of humans to CDDs has occurred after industrial accidents or in population groups (e.g., Vietnam veterans, Vietnamese, and pesticide production workers and applicators) exposed to CDD-contaminated herbicides. As stated above, the route of exposure and exposure levels cannot be exactly determined. Hepatic and dermal changes were the main effects noted, and an association between incidence of diabetes and exposure to 2,3,7,8-TCDD has been reported (Jirasek et al. 1976; USAF 1991). More toxicokinetic data for various routes of exposure with relevant congeners would be useful. These data would help in extrapolation from one route of exposure to another, since no information is available in humans on exposure via the oral route, which is the major exposure route to CDDs. The main adverse effects in animals following intermediate-duration oral and dermal exposure to 2,3,7,8-TCDD included chloracne (Allen et al. 1977; Berry et al. 1978; McNulty 1984), wasting syndrome (DeCaprio 1986; NTP 1982b; Vos et al. 1973), and liver effects (Hebert et al. 1990; NTP 1982a). Similar effects were observed with a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (NCI/NTP 1980), and 1,2,3,7,8-PeCDD and 1,2,3,4,7,8-HxCDD (Viluksela et al. 1998a, 1998b). As with acute-duration exposure, the immune system proved to be a very sensitive end point for intermediate-duration exposure to 2,3,7,8-TCDD, and an intermediate-duration oral MRL was derived from a NOAEL value for immunological effects (DeCaprio et al. 1986). No data were located regarding toxicity or toxicokinetics in animals after intermediate-duration inhalation exposure to CDDs. Information obtained from a 90-day inhalation exposure study would be relevant to people living near hazardous waste sites who may be exposed to CDDs for similar durations or much longer time periods.

Chronic-Duration Exposure and Cancer. A number of epidemiology studies have examined the toxicity of CDDs following chronic exposure to phenoxy herbicides and chlorophenols contaminated with 2,3,7,8-TCDD (Calvert et al. 1991, 1992, 1996, 1998; Cook et al. 1987b; Egeland et al. 1994; Henriksen et al. 1997; Pesatori et al. 1998; Sweeney et al. 1993). Although a number of effects have been observed, interpretation of the results is confounded by a number of factors including lack of adequate exposure information, long postexposure periods, concomitant exposure to other chemicals, and small cohorts. Follow-up medical surveillance of subjects with known past high exposure to 2,3,7,8-TCDD would provide information on the possibility that adverse effects could manifest themselves later in adult life when compounded by normal age-related changes. In addition, further research is needed in areas for which the animal data have demonstrated exposure related effects, but the human data are inconclusive. Such

research in exposed humans should focus on diseases of the circulatory system, reproductive effects, immunological effects, effects on serum lipids, and effects on thyroid function. Hepatic effects were observed in animals after chronic exposure to CDDs (including 2,3,7,8-TCDD, mixed HxCDD isomers, and 2,7-DCDD) by the oral route (NCI/NTP 1979a, 1980; NTP 1982b) and to 2,3,7,8-TCDD by the dermal route (Schwetz et al. 1973). The 2,3,7,8-TCDD congener was the most toxic. Studies in monkeys demonstrated their high susceptibility to 2,3,7,8-TCDD-induced toxicity. Developmental behavioral effects were seen in offspring of monkeys chronically exposed to low oral doses (Bowman et al. 1989a; Schantz and Bowman 1989; Schantz et al. 1992). The lowest dose tested in this series of studies was used to derive a chronic-duration oral MRL.

No studies were located regarding chronic effects of CDD exposure by the inhalation route. Toxicokinetic inhalation data and chronic-duration studies would be useful for assessing the risk levels for people living near municipal, medical, and industrial waste incinerators who can be exposed for chronic durations to CDDs by this route.

Several epidemiological studies of phenoxy herbicide and chlorophenol producers found increases in cancer mortality in populations exposed to 2,3,7,8-TCDD (Fingerhut et al. 1991; Kogevinas et al. 1993; Manz et al. 1991; Zober et al. 1990). 2,3,7,8-TCDD exposure has been especially associated with the development of soft-tissue sarcoma after a prolonged latency period (Eriksson et al. 1981, 1990; Fingerhut et al. 1991; Hardell and Eriksson 1988; Hardell and Sandrom 1979; Kogevinas et al. 1995; Smith et al. 1984a). The human data suggest that 2,3,7,8-TCDD may be a human carcinogen; however, the interpretation of many of these studies is limited by confounding factors (e.g., small cohorts, short latency periods, co-exposure to other chemicals, inadequate exposure data). Since these factors are inherent to epidemiological studies, it is unlikely that new human studies would clarify this issue. There are no reliable human studies on the carcinogenicity of other CDDs. Animal studies provided sufficient evidence that 2,3,7,8-TCDD is a carcinogen after oral (Kociba et al. 1978a; NTP 1982b; Toth et al. 1979) and dermal (Della Porta et al. 1987; Rao et al. 1988) exposure. Furthermore, 2,3,7,8-TCDD has promoting ability on tumors initiated by diethylnitrosourea (Hebert et al. 1990; Poland et al. 1982). Similarly, chronic oral exposure of rodents to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD or to 2,7-DCDD resulted in carcinogenic effects (NCI/NTP 1979a, 1980). No studies were located regarding cancer effects in animals following inhalation exposure to CDDs. However, at this time, it is unlikely that such a study would add any new information regarding the potential carcinogenicity of CDDs in animals.

Genotoxicity. Inconclusive results were obtained regarding genotoxicity of CDDs in human as well as in animal studies. Structural chromosomal changes were found in some groups of exposed individuals (Kaye et al. 1985). However, the studies were confounded by small cohorts and unknown exposures. Positive and negative results at the chromosomal level (Green et al. 1977; Loprieno et al. 1982; Meyne et al. 1985) as well as at the gene level (Randerath et al. 1989; Wahba et al. 1989) were reported in animal studies. Furthermore, negative results were obtained in dominant-lethal tests (Khera and Ruddick 1973) and sex-linked recessive-lethal tests in rats and *Drosophila* (Zimmering et al. 1985), respectively. In addition, mostly negative results were obtained in prokaryotic organisms (Geiger and Neal 1981; Gilbert et al. 1980; Toth et al. 1984). Some studies indicated that the covalent binding of 2,3,7,8-TCDD to DNA is low, and that this mechanism does not operate in CDD genotoxicity. Further studies on the mechanism of CDDs would be useful to evaluate the best possible method for detecting CDD genotoxicity.

Reproductive Toxicity. Data from studies on reproductive effects in humans (Aschengrau and Monson 1989; Egeland et al. 1994; Forsberg and Nordstrom 1985; Henriksen et al. 1996; Phuong et al. 1989a; Smith et al. 1982; USAF 1991; Wolfe et al. 1985, 1995) are inconclusive and are limited by confounding factors such as small cohorts, co-exposure to other chemicals, and inadequate exposure data. Better controlled epidemiological studies measuring 2,3,7,8-TCDD exposure levels or 2,3,7,8-TCDD body burdens would be useful to assess the human reproductive toxicity risk. Reproductive effects have been observed in oral animal studies. Increased incidences of pre- and post-implantation losses were observed in 2,3,7,8-TCDD-exposed rodents (Giavini et al. 1983; Neubert and Dillman 1972; Smith et al. 1976; Sparschu et al. 1971a), rabbits (Giavini et al. 1982), and monkeys (McNulty 1985). Adverse effects have also been observed in the reproductive organs (decreased weight), hormone levels, and gametes of male rats (Khera and Ruddick 1973; Moore et al. 1985) and non-pregnant female rats (Li et al. 1995a, 1995b). None of the acute-duration exposure studies assessed the potential of CDDs to impair fertility; data on fertility would be useful in assessing potential effects in humans exposed to CDDs for a short period of time. Reduced fertility (Bowman et al. 1989b; Hong et al. 1989; Murray et al. 1979; Schantz et al. 1992), increased incidence of abortions (Bowman et al. 1989b; Hong et al. 1989; McNulty 1984; Schantz et al. 1992), altered estrus cycle (Umbreit et al. 1987), and endometriosis (Rier et al. 1993) were observed in animals exposed for intermediate or chronic durations. Reproductive effects have also been observed in animals exposed to mixed HxCDD (Schwetz et al. 1973), but not following exposure to 2-MCDD, 2,3-DCDD, 2,7-DCDD, 1,2,3,4-TCDD, or OCDD (Khera and Ruddick 1973). Data on the reproductive toxicity of CDD following dermal exposure is limited to a single animal study which found no adverse effects on reproductive organs of mice chronically exposed to 2,3,7,8-TCDD (NTP 1982a). No animal

inhalation reproductive toxicity studies were located. Additional animal inhalation and dermal reproductive studies, particularly studies which assessed reproductive performance, would be useful to assess the possible risk in humans exposed to CDDs by these routes.

Developmental Toxicity. Studies in humans and animals indicated that 2,3,7,8-TCDD can cross the placenta and is excreted in milk (Fürst et al. 1989b; Schecter et al. 1989d, 1989g, 1990). Studies on the developmental toxicity of 2,3,7,8-TCDD in humans are inconclusive. Some studies have found significant increases in the risk of certain birth defects (Aschengrau and Monson 1990; Erickson et al. 1984; Hanify et al. 1981; Nelson et al. 1979; Phuong et al. 1989a; Wolfe et al. 1985, 1995), while other studies have found no significant alterations (Bisanti et al. 1980; Mastroiacovo et al. 1988; Townsend et al. 1982). However, a number of limitations (e.g., lack of exposure data, small sample sizes, and the lack of reliable data for birth defects prior to 2,3,7,8-TCDD exposure) limits the interpretation of the results of these studies. Epidemiology studies which measure exposure concentrations or body burdens would be useful to determine if 2,3,7,8-TCDD and other CDD congeners are human developmental toxicants. Developmental toxicity has been observed in animals orally exposed to 2,3,7,8-TCDD (Abbott and Birnbaum 1989a; Abbott et al. 1992; Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Bowman et al. 1989a, 1989b; Brown et al. 1998; Courtney 1976; Couture-Haws et al. 1991b; Giaviani et al. 1983; Gordon et al. 1995; Gray and Ostby 1995; Gray et al. 1995; Håkansson et al. 1987; Huuskonen et al. 1994; McNulty 1985; Moore et al. 1973; Neubert and Dillman 1972; Roman et al. 1998a, 1998b; Schantz et al. 1992; Silkworth et al. 1989b; Smith et al. 1976; Thomas and Hinsdill 1979; Weber et al. 1985), 2,7-DCDD (Khera and Ruddick 1973; Schwetz et al. 1973), mixed HxCDD (Schwetz et al. 1973), and OCDD (Schwetz et al. 1973). The most common effects were cleft palate, hydronephrosis, impaired development of the reproductive system, immunotoxicity, and death. No studies were located regarding developmental effects in animals after inhalation and dermal exposure. Such studies would be useful for extrapolating the possible risk to human populations exposed environmentally by these routes.

Immunotoxicity. Studies in humans did not provide conclusive evidence regarding immunotoxicity of CDDs (Ernst et al. 1998; Jansing and Korff 1994; Jennings et al. 1988; Jung et al. 1998; Mocarelli et al. 1986; Neubert et al. 1993, 1995; Reggiani 1980; Stehr et al. 1986; Svensson et al. 1994; Tonn et al. 1996; USAF 1991; Webb et al. 1989; Wolfe et al. 1985). Studies in animals indicated that CDDs are immuno-suppressive (Kerkvliet 1995). 2,3,7,8-TCDD induced thymic atrophy or thymic weight changes after oral (Hanberg et al. 1989; McConnell et al. 1978b), dermal (Hebert et al. 1990), and parenteral exposure (Gorski et al. 1988b; Olson et al. 1980a). Bone marrow degeneration was reported in orally exposed

monkeys (Hong et al. 1989). Suppressed cell-mediated and humoral immunity was found in rodents after intermediate-duration exposure (Vos et al. 1973). Similarly, immunotoxic effects were found after oral exposure of rodents to 2,7-DCDD or to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (Holsapple et al. 1986b; NCI/NTP 1980). At least in mice, differences in responsiveness to CDDs' immunotoxicity *in vivo* segregated with the Ah locus (Nagayama et al. 1989; Vecchi et al. 1983a).

Studies in animals aimed at identifying 2,3,7,8-TCDD-sensitive immune end points that can also be measured in humans would be valuable to determine correlative changes in the biomarker and immune function. However, this can be done only after establishing a database of normal values for the clinical immunology end points that may be used as biomarkers of immune-function in immunotoxicity assessments. It also important to determine in animals how well changes in lymphoid organs correlate with changes in the expression of lymphocyte subset/activation markers in peripheral blood. The role of the Ah receptor in the immunotoxicity of 2,3,7,8-TCDD needs to be researched in species other than mice. In addition, the role of Ah receptor-independent processes in 2,3,7,8-TCDD-induced immunotoxicity needs to be examined further. Such actions may include changes in intracellular calcium or in the activity of kinase/phosphatase systems, or interactions with hormone systems. A battery of immune function tests in human cohorts exposed to CDDs would be useful for detecting the immunotoxic responses in exposed individuals. The ability of CDD-exposed individuals to mount an integrated functional response to a novel antigen, such as hepatitis B vaccine, would provide a broad measure of immune function in exposed human populations.

Neurotoxicity. Studies in Vietnam veterans could not conclusively demonstrate cognitive or other central nervous system deficits (Goetz et al. 1994). Neurological examinations revealed neurological effects in humans exposed to a CDD-contaminated environment (Pocchiari et al. 1979) and in occupational settings (Goldman 1973; Jirasek et al. 1976; Klawans 1987; Pazderova-Vejlupkova et al. 1981) shortly following exposure, but reports with comparison groups do not offer clear evidence that exposure to 2,3,7,8-TCDD is associated with chronic peripheral neuropathy (Suskind and Hertzberg 1984; Sweeney et al. 1993). No notable neurological effects were found in laboratory animals after oral and dermal exposure. The existing information suggests that in adults, no long-term neurologic affects were even caused by high exposure to 2,3,7,8-TCDD-contaminated materials. However, the possibility exists that subtle central nervous system changes acquired in early adulthood could manifest themselves later in adult life when compounded by normal age-related changes in the central nervous system (Goetz et al. 1994). Thus, it would be of interest to include tests of neurological function in ongoing prospective studies of

2,3,7,8-TCDD-exposed populations to determine if neurological effects occur as the exposed population ages.

Epidemiological and Human Dosimetry Studies. Epidemiology studies have investigated the toxicity of 2,3,7,8-TCDD in populations exposed in the workplace or in the contaminated environment (after industrial accidents or herbicide spraying) (Bertazzi et al. 1993; Calvert et al. 1992, 1996, 1998; Egeland et al. 1994; Eriksson et al. 1981, 1990; Fingerhut et al. 1991; Flesch-Janys et al. 1995; Hardell and Eriksson 1988; Hardell and Sandrom 1979; Manz et al. 1991; Mastoiacovo et al. 1988; Mocarelli et al. 1991; Pesatori et al. 1993, 1998; Saracci et al. 1991; Smith et al. 1984a; Sweeney et al. 1993; Vena et al. 1998; Zober et al. 1990) and in Vietnam veterans exposed to Agent Orange (Burton et al. 1998; Henriksen et al. 1997; USAF 1991; Wolfe et al. 1985, 1995). The interpretation of the results of most of these studies is confounded by such factors as unknown levels of exposure, too short or too long postexposure periods, and small cohorts. Well conducted epidemiological and occupational studies that quantify exposure levels would be useful to assess the risk for the main end points of concern (i.e., reproductive, developmental, immunotoxic effects, and cancer). Some of the more recent studies have measured the levels of 2,3,7,8-TCDD and related compounds in serum lipid; these levels can then be used to estimate body burden at the time of exposure. There are a number of drawbacks associated with extrapolating body burdens back to the time of the original exposure using current serum 2,3,7,8-TCDD levels; these include uncertainty associated with 2,3,7,8-TCDD half-life in humans and having to use average serum 2,3,7,8-TCDD levels and average exposure durations and reference body weights and percentage of body fat. There is a lack of consensus on the half-life of 2,3,7,8-TCDD in humans, half-lives ranging from 5 to 12 years have been estimated (Pirkle et al. 1979; Schecter et al. 1994b; Wolfe et al. 1994). Additional human studies measuring 2,3,7,8-TCDD half-life would be useful in establishing dose-response relationships for human effects. All of the above limitations for assessing the body burden of 2,3,7,8-TCDD also apply to other CDDs where far less human toxicokinetic data are available. Thus, it would be useful to have congener-specific human toxicokinetic data on other CDDs and related compounds. Furthermore, human dosimetry studies would be useful in occupational settings to obtain results regarding levels of CDDs in the environment as opposed to levels in serum or adipose tissues.

Biomarkers of Exposure and Effect.

Exposure. Several studies reported results of measurements of CDD levels in the lipid fraction of adipose tissue, milk, and serum from members of the general population with unknown CDD exposure (Andrews et

al. 1989; Ryan et al. 1985a; Schecter et al. 1987b). The gas chromatography-mass spectrometry (GS/MS) tests used to detect CDD levels are sensitive and specific. Analytical testing for levels in biological fluids and tissues can be used for monitoring exposed populations. While chloracne is a known, readily identifiable effect of exposure to CDDs, it is not useful as a biomarker of exposure because of its variable expression in individuals with even very high levels of exposure to these agents. Further information on how aging and changes in body composition can influence the distribution of CDDs in tissues and body fluids would be valuable. A reverse transcriptase polymerase chain reaction method has been used to quantify CYP1A1 mRNA levels on total RNA extracts from human blood lymphocytes (Van den Heuvel et al. 1993). This method was found to be much more sensitive than, for example, measuring EROD activity, and could potentially be used as a human exposure marker for CDDs and structurally related compounds. However, EROD activity measurements can be useful as a marker of exposure to the agents.

Effect. There are no specific biomarkers of effects for CDDs. Exposure to relatively high concentrations of CDDs can lead to the development of chloracne in humans. However, while the presence of chloracne indicates CDD or similar halogenated-chemical exposure, lack of chloracne does not indicate that exposure has not taken place, as evidenced in a cohort from the Seveso incident (Mocarelli et al. 1991). Additional studies could evaluate the feasibility of using body burden as a biomarker for predicting other effects of CDDs. Although the results of an earlier study suggested that 2,3,7,8-TCDD may form adducts with DNA, albeit at an extremely low rate (Poland and Glover 1979), more recent studies that have rigorously looked for 2,3,7,8-TCDD-DNA adducts have been negative (Randerath et al. 1988; Turteltaub 1990). Expression of CYP1A1 mRNA, protein, and/or activity are sensitive biological responses in human tissues which can be observed following exposure to 2,3,7,8-TCDD and related compounds, and may be useful biomarkers of effects. Further studies to identify biomarkers of effects of CDDs would facilitate medical surveillance leading to early detection of potentially adverse health effects and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans by the inhalation and dermal routes, but data from accidentally exposed individuals suggest that exposure by these routes may lead to a significant increase in body burden of CDDs (Patterson et al. 1994; Schecter 1994b). Results from one human study indicated that more than 87% of an oral 2,3,7,8-TCDD dose in an oil vehicle was absorbed (Poiger and Schlatter 1986). Also, results from studies of absorption of CDDs from maternal milk by nursing infants showed that 90–95% of the dose of CDDs can be absorbed; hepta-substituted congeners and OCDD exhibited lower absorption rates (Abraham et al. 1994, 1996; Dahl et al. 1995; McLachlan 1993; Pluim et al. 1993b). The data indicate that 2,3,7,8-TCDD

is effectively absorbed and that absorption is vehicle-dependent (Fries and Marrow 1975; Lucier et al. 1986; Poiger and Schlatter 1980); oil vehicles were most effective (Olson et al. 1980b; Piper et al. 1973). Transpulmonary absorption of 2,3,7,8-TCDD also occurs in animals (Diliberto et al. 1996; Nessel et al. 1992). Dermal absorption of 2,3,7,8-TCDD in rats was found to be age-dependent (Banks et al. 1993). In rats, following single equivalent intratracheal, oral, and dermal 2,3,7,8-TCDD doses, absorption was calculated as 95, 88, and 40% of the administered dose, respectively (Diliberto et al. 1996). The available information shows that absorption of 2,3,7,8-TCDD has been fairly well characterized in animals.

Based on analysis of CDDs in adipose tissue, milk, and blood, it appears that humans store exclusively 2,3,7,8-chlorine substituted congeners (Fürst et al. 1987; Rappe et al. 1987; Van den Berg et al. 1986b). Data are available on tissue distribution of 2,3,7,8-TCDD in rats after inhalation, oral, and dermal exposure (Diliberto et al. 1996). The liver and adipose tissue are the major storage sites in animals. In general, distribution of CDDs is congener specific, and depends on the dose and route of administration (Diliberto et al. 1996; Van den Berg et al. 1994). Age was also a factor in the distribution of 2,3,7,8-TCDD in mice (Pegram et al. 1995). The distribution of 2,3,7,8-TCDD-derived radioactivity in subcellular liver fractions has also been studied (Santostefano et al. 1996). 2,3,7,8-Chlorine substituted CDDs are the predominant congeners retained in tissue and body fluids from humans, rodents, and monkeys (Abraham et al. 1989c; Van den Berg et al. 1983). Further dosimetry studies of various durations in which levels of 2,3,7,8-TCDD and related compounds are monitored in tissues suspected of being targets for 2,3,7,8-TCDD toxicity would provide valuable information. These data can be used to establish correlations between target-tissue doses and adverse effects.

Data regarding the biotransformation of CDDs in humans are limited to a self-dosing experiment that provided some evidence that 2,3,7,8-TCDD is partially excreted in the feces in the form of metabolites (Wendling et al. 1990). The use of human cell systems in culture might be considered a useful addition to whole-animal studies for examining the metabolic fate of CDDs. Biotransformation of CDDs has been examined in several species, but the structure of metabolites has been elucidated only in the rat and dog (Poiger and Buser 1984). Although information regarding metabolism following inhalation or dermal exposure is lacking, there is no reason to believe that different pathways would operate after exposure by these routes.

Only one study was located that provide limited evidence of fecal excretion of 2,3,7,8-TCDD metabolites in adult humans (Wendling et al. 1990). Several studies provided information regarding fecal excretion of

CDDs in infants exposed through breast milk (Abraham et al. 1994; McLachlan 1993; Pluim et al. 1993b). Elimination of CDDs through maternal milk is well documented (Fürst et al. 1994; Rappe et al. 1985; Schecter and Gasiewicz 1987a; Schecter et al. 1989d, 1989e). Fecal excretion is the main route of excretion of CDDs in animals after all routes of exposure (Diliberto et al. 1996). Estimates of 2,3,7,8-TCDD half-life in humans are available (Pirkle et al. 1989; Poiger and Schlatter 1986; Wolfe et al. 1994), but further information regarding the relationships between aging, fat redistribution, and half-lives in humans would be valuable.

Comparative Toxicokinetics. CDDs are efficiently absorbed from the gastrointestinal tract of mammals, but the vehicle plays an important role (Olson et al. 1980b; Piper et al. 1973; Poiger and Schlatter 1986; Van den Berg et al. 1987c). Distribution data in orally exposed rodents indicated that the highest postexposure levels were in the liver followed by the fat (Diliberto et al. 1996; Khera and Ruddick 1973; Olson 1986), but distribution is highly dose- and species-dependent. The studies to date suggest that compared with rodents, primates, including humans, accumulate significantly less CDDs in the liver than in adipose tissue (Neubert et al. 1990a; Ryan et al. 1986; Van Miller et al. 1976). With the exception of the guinea pig, mammals retain only 2,3,7,8-substituted congeners. The high liver retention of 2,3,7,8-substituted congeners by rodents has been attributed to the presence of inducible storage sites, presumably CYP1A2 (Leung et al. 1990b). In all mammalian species studied, exposure by breast-feeding has a much greater contribution to the offspring 2,3,7,8-TCDD body burden than placental transfer. Metabolic capacities are species-dependent. Rats, hamsters, and mice metabolize and eliminate CDDs much faster than the guinea pig. The metabolites were excreted predominantly via the bile and feces, with minor amounts excreted in the urine in all species (Diliberto et al. 1996; Fries and Marrow 1975; Weber and Birnbaum 1985). Whole-body half-lives ranged from 11 days in hamsters (Olson et al. 1980b) to more than 1 year in monkeys (Bowman et al. 1989b; McNulty et al. 1982), and approximately 7–12 years in humans (Wolfe et al. 1994). The toxicity of CDDs has been associated with the parent compound and not the metabolites (Mason and Safe 1986a; Weber et al. 1982); therefore, metabolism and excretion represent a detoxification process. The data collected in recent years indicate differences in species susceptibility to CDDs cannot be explained by differences in toxicokinetics alone; it is likely that genetic factors have an important role. Based on this information, species-, congener-, and dose-specific toxicokinetic data need to be factored in human risk assessment for CDDs. Several models that describe the disposition of 2,3,7,8-TCDD in animals and humans were identified from the literature (Andersen et al. 1993, 1997a, 1997b; Carrier et al. 1995a, 1995b; Kissel and Robarge 1988; Kohn et al. 1993; Leung et al. 1988,

1990b). Although each new model that is published usually fills data gaps identified in earlier models, further research is necessary to increase their reliability for use in human risk assessment.

Methods for Reducing Toxic Effects. The mechanism by which CDDs enter the blood stream in humans is not known; consequently, there are no established methods for reducing absorption. In experimental animals, however, administration of a diet containing activated charcoal reduced mortality in an acute-duration study presumably by preventing gastrointestinal absorption and the reabsorption of the chemical from biliary secretions (Manara et al. 1984). Identification of additional substances that could prevent or delay absorption and that do not represent a toxic risk *per se* would be valuable. Increasing the fact content of the diet by ingesting non-absorbable lipids has been suggested as a method for increasing the elimination rate (Rohde et al. 1997). These authors estimated that if the normal feces excretion of 5 g fat/day was quadrupled and the lipid based distribution of CDDs/CDFs between the body and the intestine stayed the same, the overall elimination rate would at least double. There are no established methods for reducing body burden in humans, but data from a study of Vietnam veterans suggested that persons with more fat tend to eliminate 2,3,7,8-TCDD more slowly (Wolfe et al. 1994). It was suggested that metabolic or other factors that change with age (i.e., redistribution of fat stores) affect 2,3,7,8-TCDD elimination. Studies examining the effect of fasting in animals exposed to CDDs would provide useful information that can be used to characterize the effectiveness of this approach better. Although, in recent years, great advances have been made related to the understanding of the mechanism of action of CDDs, no methods exist to block the toxic response due to exposure to CDDs. Further characterization of the Ah receptor protein and understanding of physiological effects of interfering with the chain of events that follow binding of CDDs to the Ah receptor would be useful for the possible identification of blockers of those events. Further studies aimed at elucidating the non Ah receptor-mediated mechanisms of action of CDDs would also be valuable. There are no established methods for mitigation of health effects resulting from exposure to CDDs.

Children's Susceptibility. A limited number of human studies have examined health effects of CDDs in children. Data from the Seveso accident suggest that children may be more susceptible to the dermal toxicity of 2,3,7,8-TCDD (chloracne), but it is not known if this would be the case for other effects. Follow-up medical surveillance of the Seveso children (including measurement of serum 2,3,7,8-TCDD levels) would provide information on whether childhood exposure would pose a risk when the individual matures and ages. The available human and animal data provide evidence that 2,3,7,8-TCDD can cross the placenta and be transferred to an infant via breast milk. Although information on the developmental

toxicity of CDDs in humans is limited, there are extensive animal data that the developing organism is very sensitive to the toxicity of 2,3,7,8-TCDD. Several human studies have found significant alterations in markers of liver, thyroid, immune, and neurological function in young breast-fed infants of mothers with higher current background or general population CDD levels. Recent data suggest that the neurological effects are reversible; prospective studies of the breast-fed individuals would provide useful information on whether these children are at risk of developing additional effects as they age. Further data needs relating to developmental effects are discussed above under Developmental Toxicity.

In general, the available toxicokinetic data did not examine potential differences between adults and children; toxicokinetic studies examining how aging and changes in body composition can influence distribution and turnover rates would be useful in assessing children's susceptibility to CDD toxicity. Most of the available mechanism of action data suggest that the toxicity of 2,3,7,8-TCDD is mediated through the Ah receptor. We do not know if there are any age-related differences in receptor binding or expression; studies in animals would be valuable to fill this information gap. No age-specific biomarkers of exposure or effect were identified for CDDs; the long half-life of 2,3,7,8-TCDD in humans, suggests that there may not be a way to assess whether adults were exposed as children to 2,3,7,8-TCDD. Additionally, there are no data to determine whether there are any interactions with other chemicals which would be specific for children. There is very little available information on methods for reducing 2,3,7,8-TCDD toxic effects or body burdens; it is likely that research in adults would also be applicable to children.

Child health data needs relating to exposure are discussed in Section 5.8.1, Identification of Data Needs: Exposures of Children.

2.11.3 Ongoing Studies

Ongoing studies regarding the health effects of CDDs were reported in the Federal Research in Progress File (FEDRIP 1998). Table 2-18 presents a summary of this information.

Table 2-18. Ongoing Studies on CDDs

Investigator	Affiliation	Research description	Sponsor
RL Allen	Hybrizyme Corp., Research Triangle Park, NY	This project will complete the development of a cost-effective assay system for the detection of dioxin-like compounds that incorporates the human Ah-receptor	NIEHS
NZ Alsharif	Creighton University, Omaha, NE	Data from this study will provide a clear indication of the role of oxidative stress in the chronic toxicity of TCDD including its most sensitive target, the immune system	NIEHS
DA Bell	NIEHS	Explore genetic variability in the metabolism of carcinogens such as 2,3,7,8-TCDD	
L Bernstein	University of Southern California	Conduct a case-control study which examines the association of serum organochlorine residue levels with the risk of breast cancer among African-American women	
L F Bjeldanes	University of California San Diego	Identification and characterization of mechanisms of action of food-borne antitoxicants in rats, trout, and murine hepatoma cell lines	
JA Boyd	National Institute of Environmental Health Sciences (NIEHS	Perform a molecular genetic analysis of pathologic conditions of the human uterus, resulting from exposure to chemicals such as 2,3,7,8-TCDD	
CA Bradfield	Northwestern University	Develop new models of the Ah receptor signaling pathway and using transgenic mouse lines to identify the molecular basis of species dependent responses to 2,3,7,8-TCDD; cloning the cDNAs which encode the Ah receptor from a variety of murine strains and animal models	
TP Brent	St. Jude Children's Research Hospital	Develop histochemical assays for MGMT (O6-alkylguanine-DNA alkylt-ransferase, previously called GATase) expression in human tumor and tissue preparations Detailed analysis of the structure, function, and regulation of MGMT activity will ultimately enable the to prediction of tumor resistance, as well as an individual's susceptibility to carcinogenesis induced by chemicals such as 2,3,7,8-TCDD	

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
AL Bunge	Colorado School of Mines, Golden, CO	Develop algorithms which predict the absorbed dose following dermal exposure to chemically contaminated soils	NIEHS
SW Burchiel	University of New Mexico Albuquerque, Albuquerque, NM	Examine the influence of environmental chemicals on human breast epithelial cell growth and signaling associated with endogenous growth-factor receptors	
DL Busbee	Texas A&M University	Evaluate the induction of cytochrome P-4501A1 in human and animal cells by a series of aromatic and halogenated aromatic hydrocarbons; he is also examining whether prior exposure to PAHs significantly alters the amount and type of DNA damage initiated by mutagens in human and rodent cells	
KW Brown	Texas A&M University	Utilize bioassays, mammalian cell cultures, and human lymphocyte cultures to measure the genotoxicity, immunotoxicity, developmental toxicity, and 2,3,7,8-TCDD-induced toxicity of sample extracts from Superfund sites;	
KW Brown and KC Donnelly	Texas A&M University	Develop a comprehensive laboratory testing procedure for evaluating the acute and chronic toxicity of complex environmental mixtures	
MJ Connor	University of California Los Angeles, Los Angeles, CA	Investigation of the mechanisms involved in the expression of 2,3,7,8-TCDD induced toxicity in congenic haired and hairless HRS/J mice	
K Cooper	Rutgers University, New Brunswick, NJ	Evaluate the affects of a number of different compounds: dioxins, dibenzofurnas, oil and estrogenic compounds on both invertebrates and vertebrate species	U. S. Department of Agriculture Cooperative State Research Service
MS Denison	University of California San Diego	Investigations of the molecular mechanisms of action of 2,3,7,8-TCDD in mouse hepatoma cells	
RL Dickerson, GP Cobb, and G Birrenkott	Clemson University	Determine the impact of low levels of 2,3,7,8-TCDD on productivity of White Leghorns chickens and are developing non-lethal techniques for measuring effects in chickens	

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
B Eskenazi	University of California Berkeley, Berkeley, CA	Follow-up the Seveso cohort and examine their risk of endometriosis and other related reproductive endpoints hypothesized to be dose-related to serum levels of TCDD	NIEHS
VJ Feil, JK Huwe, and H Hakk	Agricultural Research Service, Fargo, ND	Identify and quantitate residues of chlorinated organics (congeners of 2,3,7,8-TCDD, furans, and PCBs) in beef and milk, and in animal feeds and certain forages	U. S. Department of Agriculture Agricultural Research Service
PK Freeman	Oregon State University	Determine the mechanistic features of the photodegradation of 2,3,7,8-TCDD in mice	
GF Fries and LS Willett	Ohio Agricultural Research and Development Center	Develop models of the transport of 2,3,7,8-TCDD contained in feeds and other environmental matrices to beef intended for human consumption	
GF Fries	Beltsville Agricultural Research Center	Refine a model for simulation of persistent residues such as 2,3,7,8-TCDD in pigs from weaning through marketing; in growing beef cattle, including the fattening phase; and in dairy cattle during lactation	
TA Gasiewicz	University of Rochester Medical Center	Utilize an *in vivo* bone marrow-thymus reconstitution model and mouse strains with arrested T-cell development to define the cellular and molecular targets of 2,3,7,8-TCDD that lead to thymic atrophy, and determine how these events relate to its overall action on the immune system. Dr. Gasiewicz is also determining what controls the functional activity of the Ah receptor, what target genes are affected in sensitive tissues, and how the modulated expression of these genes leads to the toxic responses observed after exposure to 2,3,7,8-TCDD	
J P Giesy	Michigan State University	Assess the acute and chronic effects of trace contaminants on aquatic organisms using mechanistic and statistical models for predicting the fates of trace contaminants	U. S. Department of Agriculture Cooperative State Research Service

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
WF Greenlee	University of Massachusetts Medical School	Examine the role of the Ah receptor and its known differentiation and growth regulatory genes in the development and function of the thymic microenvironment. The studies use early gestation C57BL/6 and neonatal SCID mice and fetal thymic organ cultures as models.	
M Hahn	Boston University	Utilize fish to investigate the mechanisms of animal sensitivity and resistance to 2,3,7,8-TCDD and related planar halogenated aromatic hydrocarbons (PHAH), especially the resistance which develops after long-term (multi-generation) exposure associated with hazardous waste sites	
ME Hahn	Woods Hole Oceanographic Institution, Woods Hole, MA	Characterize the structure, function, regulation, and evolutionary relationships of the Ah receptor in non-mammalian species, particularly fish	
O Hankinson	University of California Los Angeles, Los Angeles, CA	Use transgenic mouse technology to address the potential role of the Ah receptor nuclear translocator (Arnt) protein in carcinogenesis and in developmental processes	
O Hankinson	University of California Los Angeles, Los Angeles, CA	*In vitro* mutagenesis experiments performed on the Ah receptor nuclear translocator (Arnt) protein in order to identify putative functional domains, including domains for nuclear translocation, for binding the ligand-binding subunit, for binding the XRE, and for transcriptional activation	
EA Hassoun	Creighton University	Study the teratogenicity and fetotoxicity of two polyhalogenated cyclic hydrocarbons (PCH) (endrin and lindane), as compared with that induced by 2,3,7,8-TCDD, in the fetuses of pregnant C57BL/6J (TCDD-responsive) and DBA/2J (TCDD-non-responsive) mice	
M Hejtmancik	Battelle Memorial Institute, Columbus, OH	Test the hypotheses: The USEPA interim TEFs for dioxins, dibenzofurans and PCBs can predict the relative carcinogenic potency of single congeners in female Sprague-Dawley rats	NIEHS

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
A Hendricks	University of California Davis	Test the utility of *in vivo* biomarkers for detecting and characterizing reproductive toxicity of 2,3,7,8-TCDD in experiments with a non-human primate model	
MH Hooper	University of Washington	Characterize biomarkers for toxic substances in wildlife populations inhabiting hazardous waste sites	
RJ Hutz	University of Wisconsin-Milwaukee, Milwaukee, WI	Utilize female rats to determine whether 2,3,7,8-TCDD exerts its antifertility effects by modulating the action of estrogen at the ovary	
AK Jaiswal	Fox Chase Cancer Center	Elucidate the molecular mechanisms that control the basal level of expression in normal and tumor cells, induction and transcription due to xenobiotics such as 2,3,7,8-TCDD, and tissue-specific and developmental expression of NQOI and NQO2 genes in rat tissues	
MO James	University of Florida, Gainesville, FL	Test the hypotheses that two Ah receptor agonists found in Superfund sites, namely 2,3,7,8-TCDD and 3,3',4,4'-TCB cause alterations in the physiological and structural make-up of intestinal cells that affect the intestinal bioavailability and biotransformation of lipophilic chemicals	NIEHS
CR Jeffcoate	University of Wisconsin-Madison, Madison, WI	Elucidate mechanisms of regulation of CYP1B1 gene transcription and see if the AhR is involved in this regulation	National Cancer Institute
NE Kaminski	Michigan State University	Determine 2,3,7,8-TCDD's relative effects on B-cell proliferation and differentiation using B-cells from $B6C3F_1$ mice	
HK Kang	Department of Veterans Affairs Medical Center, Washington, DC	Perform a retrospective cohort mortality study to determine the overall mortality rate as well as the cause-specific mortality rates associated with Vietnam service or exposure to Agent Orange in 10,000 Marines who served in Vietnam and an equal number of those who served elsewhere	Department of Veterans Affairs Research and Development
NI Kerkvliet	Oregon State University	Perform a series of studies investigating cytokine production in 2,3,7,8-TCDD-treated mice	

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
NI Kerkvliet	Oregon State University	Characterize the enhanced T cell activation induced by 2,3,7,8-TCDD as it relates to the suppression of antigen-specific immune responses	
AT Kong	University of Illinois at Chicago, Chicago, IL	Isolate and characterize the genes encoding for two major types of UDP-glucuronosyltransferases (UGTs) in mice to gain insights into the biological mechanisms of detoxification and/or toxicity of different carcinogens catalyzed by UGTs in the mouse	
CA Lamartiniere	University of Alabama at Birmingham, Birmingham, AL	Investigate the potential of environmental chemicals for altering susceptibility for breast cancer in Sprague Dawley CD rats exposed during three critical periods of development	NIEHS
RG Lindahl	University of South Dakota	Elucidate and characterize the mechanisms responsible for tissue-specific differential gene expression in rat in liver and hepatoma cells so as to understand the molecular basis of gene expression under normal and pathophysiological (i.e., following both xenobiotic exposure [to 2,3,7,8-TCDD or 3-methylcholantherene] and during hepatocarcinogenesis) conditions	
G Lucier	NIEHS	Determine dose-response relationships for 2,3,7,8-TCDD following chronic exposure in rodent models and, accidental or occupational exposure in humans	
MI Luster	NIEHS	Employ a variety of *in vivo* and *in vitro* techniques to study the adverse effects on the immune system resulting from exposure to environmental chemicals such as 2,3,7,8-TCDD	
BV Madhukar	Michigan State University	Use embryo and fetal cell cultures to determine if remediation of several classes of mixtures of environmental toxicants (PCBs, HAHs, PAHs) decreases the toxicities of the parent mixtures or actually enhances the toxicities	

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
F Matsumura	University of California Davis	Study the acute and chronic effects of 2,3,7,8-TCDD on adipose lipoprotein lipase (LPL) in guinea pigs	
F Matsumura	University of California Davis	Determine the toxicological consequences of elevated protein tyrosine kinase activities in guinea pigs and mice and why 2,3,7,8-TCDD causes such an effect on EGF receptors	
JL Napoli	State University of New York (SUNY) at Buffalo, NY	Determine whether 2,3,7,8-TCDD causes functional vitamin A abnormalities by altering the steady-state concentrations of retinoic acid and/or RAR/RXR in male and female rat and male Syrian golden hamster tissues	
DW Nebert	University of Cincinnati, Cincinnati, OH	Utilize human transgenic mouse lines to define the precise role of the human Ah receptor in studies of toxicity and cancer caused by 2,3,7,8-TCDD and other environmental chemicals	
JL Newsted	University of Massachusetts Medical School	Develop methodologies utilizing white sucker fish to evaluate the impact of xenobiotics on ecosystem health	
PW O'Keefe	State University of New York SUNY, Albany, NY	Determine the complete range of toxic compounds in the sediment collected near an aluminum plant in the Massena area of the St. Lawrence River	
JR Olson	State University of New York (SUNY) at Buffalo, NY	Develop mechanism-based molecular and biochemical markers of exposure, effect, and/or susceptibility specific to 2,3,7,8-TCDD in maternal and fetal rat liver, placenta, and lymphocytes	
GH Perdew	Purdue University	Use tissue and cell cultures to examine the multiple mechanisms of Ah receptor regulation and seeks to determine the biochemical events from initial synthesis and assembly to translocation into the nucleus. Dr. Perdew is also examining the biochemical properties of the Ah receptor-ligand complex that affect its overall regulation.	
DH Petering	University of Wisconsin-Milwaukee, Milwaukee, WI	Utilize aquatic organisms to study the mechanism of action (i.e, target-organ specificity, regulation of cytochrome P-450 expression) of 2,3,7,8-TCDD	

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
RE Peterson	University of Wisconsin-Madison, Madison, WI	Determine the mechanisms by which 2,3,7,8-TCDD adversely affects the male reproductive system of rats exposed in adulthood or during fetal and neonatal development;	
AP Poland	University of Wisconsin-Madison, Madison, WI	Seek to characterize the Ah receptor in the mouse and is screening lower vertebrate and invertebrate species for the presence of the Ah receptor	
CJ Portier	NIEHS	Increase the use and application of mathematical and statistical models in toxicology and biochemistry and to implement new mathematical models to help explain current research findings relating to carcinogenesis and suppressed immune function following exposure to toxicants such as 2,3,7,8-TCDD	
A Puga	University of Cincinnati, Cincinnati, OH	Elucidate the biological responses (i.e., gene expression patterns) to 2,3,7,8-TCDD in mice	
SM Puhvel	Department of Veterans Affairs Medical Center	Study the effect that 2,3,7,8-TCDD has on human skin (i.e., the biochemical mechanisms involved in the induction of chloracne)	
K Randerath	Texas A&M University	Measure chemical DNA alterations in exposed experimental animals, humans, and cultured cells induced by exposure to aromatic and halogenated aromatic hydrocarbons, reconstituted mixtures from these compound classes, and field extracts of wood-preserving and oily waste dump sites;	
DJ Reed	Oregon State University	Examine the mechanisms of toxicity of selected bioenvironmental chemicals, especially halocarbons	
RH Rice	University of California San Diego	Establish a new short-term test for toxic agents using human epidermal cells	
RH Rice	University of California Davis	Utilize guinea pigs to develop bioassays for the detection of 2,3,7,8-TCDD and other hazardous agents	

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
RH Rice	University of California Davis	Utilize human tissues to investigate the posttranslational modifications to which the enzyme keratinocyte transglutaminase (TGK) is subject, and its transcriptional regulation by effectors such as 2,3,7,8-TCDD	
AB Rifkind	Cornell University Medical Center, Ithaca, NY	Use a chick embryo model to investigate whether 2,3,7,8-TCDD-induced P-450 participates in 2,3,7,8-TCDD toxicity by metabolizing endogenous compounds, such as the membrane fatty acid, arachidonic acid (AA), to biologically active metabolites that can affect cell signals and thereby modulate toxicity	
RA Roeder and MJ Garber	University of Idaho	Develop baseline data regarding the incidence and quantities of PCDD/PCDFs in soft tissues and milk from cattle and determination of the relationship between feeding practices and the presence of PCDD/PCDFs in soft tissues and milk	
SH Safe	Texas A&M University	Conduct several interrelated studies with individual polycyclic aromatic hydrocarbons (PAHs) and reconstituted PAH mixtures to determine the interactions of these compounds and the role of these interactions in PAH-induced carcinogenicity	NIEHS
AE Silverstone	State University of New York SUNY, Syracuse, NY	Determine how activation of the Ah receptor or the ER can lead to thymic atrophy and the appearance of T-cells that could promote autoimmune disease in selected mouse strains	
KT Shiverick	University of Florida, Gainesville, FL	Investigate mechanisms by which the chlorinated hydrocarbons 2,3,7,8-TCDD and PCBs have disruptive effects on placental- uterine function	NIEHS
P Sinclair	Department of Veterans Affairs Medical Center, White River Junction, VT	Determine the mechanism by which 2,3,7,8-TCDD and related planar PAHs cause massive liver accumulation of uroporphyrin (URO)	

Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
PR Sinclair	Dartmouth College	Investigate the mechanisms of uroporphyrinogen (UROgen) oxidation and the inhibition of UROgen decarboxylase (URO-D), which are among the toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and other planar polyhalogenated hydrocarbons (in hepatocyte cultures and in intact animals, mice and guinea pigs)	
G S Smith	New Mexico State University	Utilize rats, sheep, and/or cattle to study the disposition of selected xenobiotics such as 2,3,7,8-TCDD and protocols that might enhance tolerance	
MB Solomon and LB Willett	Ohio Agricultural Research and Development Center, Wooster, OH	Develop models of the transport of dioxins contained in feeds and other environmental matrices to beef intended for human consumption	U. S. Department of Agriculture Agricultural Research Service
GM Stancel	University of Texas	Examine how developmental exposure of rodents to toxicants such as 2,3,7,8-TCDD disrupt gene expression and produce cellular defects	
TR Sutter	Johns Hopkins University	Elucidate the events that occur in humans exposed to Ah receptor agonists and determine whether effects of 2,3,7,8-TCDD are caused by the altered expression of specific subsets of Ah receptor-regulated genes	
WA Toscano	Tulane University	Determine the biochemical basis underlying 2,3,7,8-TCDD toxicity	
JW Tracy	the University of Wisconsin-Madison, Madison, WI	Determine whether 2,3,7,8-TCDD and oltipraz induce glutathione S-transferase gene expression in *S. mansoni*	
RH Tukey	University of California San Diego	Investigate the cellular events involved in the regulation of the mouse AhR *in vivo*	

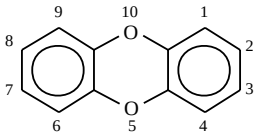
Table 2-18. Ongoing Studies on CDDs (continued)

Investigator	Affiliation	Research description	Sponsor
C Vandevoort	University of California Davis	Evaluate the function of human and macaque granulosa, trophoblast and endometrial cells, and macaque embryos in response to 2,3,7,8-TCDD while being cultured *in vitro,* and the cellular mechanisms by which primate reproductive cells sustain toxic damage	
RJ Van Beneden	University of Maine	Examine the molecular mechanisms of tumorigenesis in clams exposed to 2,3,7,8-TCDD-containing sediments	
WM Weston	Thomas Jefferson University	Identify the regulatory elements associated with abnormal palate development in the mouse	
JP Whitlock	Stanford University	To understand the mechanisms by which mammalian cells adapt to environmental exposures and the mechanisms by which environmental exposures produce toxicity	NIEHS
LB Willett	Ohio State University, Wooster, OH	Cattle: methods to detect and monitor occurrence of potentially hazardous xenobiotics in their environment; methods to reduce or eliminate exposure; determine mechanisms by which xenobiotics are transported, bound, and mobilized; study target organ modification caused by xenobiotic chemicals	U. S. Department of Agriculture Cooperative State Research Service
MS Wolff	Mount Sinai School of Medicine of CUNY, New York, NY	Provide analyses for PAH and TCDD compounds that are environmentally important and that may contribute significantly to the assays to be done	NIEHS

NIEHS = National Institute of Environmental Health Sciences

3. CHEMICAL AND PHYSICAL INFORMATION

CDDs are a class of related chlorinated hydrocarbons which are structurally similar. The basic structure is a dibenzo-*p*-dioxin (DD) molecule, which is comprised of 2 benzene rings joined at their *para* carbons by 2 oxygen atoms. There are 8 homologues of CDDs, monochlorinated through octachlorinated. The class of CDDs contains 75 congeners, consisting of 2 monochlorodibenzo-*p*-dioxins (MCDDs), 10 dichlorodibenzo-*p*-dioxins (DCDDs), 14 trichlorodibenzo-*p*-dioxins (TrCDDs), 22 tetrachlorodibenzo-*p*-dioxins (TCDDs), 14 pentachlorodibenzo-*p*-dioxins (PeCDD), 10 hexachlorodibenzo-*p*-dioxins (HxCDDs), 2 hepta-chlorodibenzo-*p*-dioxins (HpCDDs), and a single octachlorodibenzo-*p*-dioxin (OCDD) (Ryan et al. 1991). The general structure of the dibenzo-*p*-dioxins is shown below. The numbers indicate the positions for chlorine substitutions, excluding, of course, positions 5 and 10.



Not all congeners have been studied for their chemical and physical properties, but basic properties are known for the CDDs as a chemical family and for the homologous groups. Chlorinated dioxins exist as colorless solids or crystals in the pure state. They have a low solubility in water and a low volatility. Chlorinated dioxins have an affinity for particulates and readily partition to particles in air, water, and soil. The more toxic compounds appear to be the 2,3,7,8-substituted tetra-, penta-, and hexachloro compounds (i.e., 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD). These are also the congeners, along with OCDD, that have the greatest tendency to bioaccumulate. One of the most toxic congeners in mammals is believed to be 2,3,7,8-TCDD; this compound has also been the most studied of the TCDD congeners.

3.1 CHEMICAL IDENTITY

Information regarding the chemical identities of CDDs is presented in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of CDDs is presented in Table 3-2.

Table 3-1. Chemical Identity of CDDs[a]

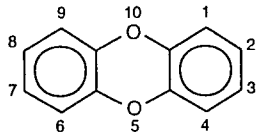
Characteristic	Monochlorodibenzo-p-dioxins	Dichlorodibenzo-*p*-dioxins
Chemical Name	1-Chlorodibenzo-p-dioxin (CAS #39227-53-7); 2-Chlorodibenzo-p-dioxin (CAS #39227-54-8) [b]	2,7-Dichlorobenzo-p-dioxin(CAS #33857-26-0)[e]
Synonym(s)[j]	1-Chlorodibenzo-p-dioxin; 1-Chlorodibenzo-p-dioxin; 1-Chlorodibenzo[b,e](1,4)dioxin[c]; 2-Chlorodibenzo(b,e)(1,4)dioxin[b]	1,3- or 1,6- or 2,3- or 2,7- or 2,8-Dichlorodibenzo-p-dioxin; 1,3- or 1,6- or 2,3- or 2,7- or 2,8-Dichlorodibenzo[b,e](1,4)dioxin; 1,3- or 1,6- or 2,3- or 2,7- or 2,8-Dichlorodibenzodioxin[b]
Total number of possible isomers	2	10
Registered trade name(s)	No data	No data
Chemical formula	$C_{12}H_7ClO_2$[c]	$C_{12}H_6Cl_2O_2$[b]
Chemical structure[b,f]		See footnote "f"
Identification numbers:[h]		
CAS registry	39227-53-7 (1-)[c] 39227-54-8 (2-)[b]	50585-39-2 (1,3-); 38178-38-0 (1,6-); 29446-15-9 (2,3-)[c]; 33857-26-0 (2,7-)[e]; 38964-22-6 (2,8-)[c]
NIOSH RTECS	HP3095300 (1-); HP3095500 (2-)[c]	HP3095700 (1,3-); HP3095800 (1,6-); HP3096000 (2,3-)[c]; HP3100000 (2,7-)[e]; HP3150000 (2,8-)[c]
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	No data	4124 (2,7-)[e]
NCI	No data	CO3667 (2,7-)[e]

Table 3-1. Chemical Identity of CDDs[a] (continued)

Characteristic	Trichlorodibenzo-*p*-dioxins	Tetrachlorodibenzo-p-dioxins[g]
Chemical name	1,2,4-Trichlorodibenzo-p-dioxin (CAS # 39227-58-2); 2,3,7-Trichlorodibenzo-p-dioxin (CAS # 33857-28-2)[b]	2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS # 1746-01-6)[e]
Synonym(s)[j]	1,2,4- or 2,3,7-Trichlorodibenzo-para-dioxin; 1,2,4- or 2,3,7-Trichlorodibenzo[b,e](1,4)dioxin; 1,2,4- or 2,3,7-Trichlorodibenzodioxin[b]	1,2,3,4- or 1,2,3,8- or 1,3,6,8- or 1,3,7,8- or 1,2,7,8- or 2,3,7,8-Tetrachlorodibenzo-p-dioxin[d]; 1,2,3,4- or 1,2,3,8- or 1,2,7,8- or 1,3,6,8- or 1,3,7,8- or 2,3,7,8-Tetrachloro-dibenzodioxin; 1,2,3,4- or 1,2,3,8- or 1,3,6,8- or 1,3,7,8- or 1,2,7,8- or 2,3,7,8-Tetrachlorodibenzo[b,e](1,4)dioxin; 1,2,7,8- or 2,3,7,8-Tetrachlorodibenzo-1,4-dioxin; 2,3,6,7-Tetrachloro-dibenzodioxin; 1,2,7,8-Tetrachlorodi-benzo-p-dioxin; Dioxin; TCDBD; TCDD[b]
Total number of possible isomers	14	22
Registered trade name(s)	No data	No data
Chemical formula	$C_{12}H_5Cl_3O_2$[e,i]	$C_{12}H_4Cl_4O_2$[b]
Chemical structure[b,f]	See footnote "f"	See footnote "f"
Identification numbers:[h]		
CAS registry	39227-58-2 (1,2,4-); 33857-28-2 (2,3,7-)[c]	30746-58-8 (1,2,3,4-); 53555-02-5 (1,2,3,8-); 34816-53-0 (1,2,7,8-); 33423-92-6 (1,3,6,8-); 50585-46-1 (1,3,7,8-)[c] **1746-01-6 (2,3,7,8-)[e]**
NIOSH RTECS	HP3530000 (1,2,4-); HP3630000 (2,3,7-)[c]	HP3493000 (1,2,3,4-); HP3494000 (1,2,3,8-); HP3494500 (1,2,7,8-); HP3495000 (1,3,6,8-); HP3495500 (1,3,7,8-)[c]; **HP3500000 (2,3,7,8-)[e]**
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	No data	4151 (2,3,7,8-)[e]
NCI	No data	C03714 (2,3,7,8-)[e]

Table 3-1. Chemical Identity of CDDs[a] (continued)

Characteristics	Pentachlorodibenzo-p-dioxins	Hexachlorodibenzo-p-dioxins
Chemical name	1,2,3,7,8-Pentachlorodibenzo-p-dioxin (CAS #40321-76-4) [c]	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin (CAS #57653-85-7); 1,2,3,7,8,9- Hexachlorodibenzo-p-dioxin (CAS #19408-74-3); Hexachlorodibenzo-p-dioxin (CAS #34465-46-8)[e]
Synonym(s)[j]	1,2,3,4,7- or 1,2,3,7,8- or 1,2,4,7,8-Pentachlorodibenzo-para-dioxin; 1,2,3,4,7- or 1,2,3,7,8- or 1,2,4,7,8-Pentachlorodibenzodioxin; 1,2,3,4,7- or 1,2,3,7,8- or 1,2,4,7,8-Pentachlorodibenzo[b,e] (1,4)dioxin[b]	1,2,3,4,7,8- or 1,2,3,6,7,8- or 1,2,3,6,7,9- or 1,2,3,7,8,9- or 1,2,4,6,7,9-Hexachlorodi-benzo-para-dioxin; 1,2,3,4,7,8- or 1,2,3,6,7,8- or 1,2,3,6,7,9- or 1,2,3,7,8,9- or 1,2,4,6,7,9-Hexachlorodibenzodioxin[b]; Hexachloro-dibenzo(b,e) (1,4)dioxin[i]; Hexachlorodibenzo-4-dioxin[e]
Total number of possible isomers	14	10
Registered trade name(s)	No data	No data
Chemical formula	$C_{12}H_3Cl_5O_2$[c]	$C_{12}H_2Cl_6O_2$[b]
Chemical structure[b,f]	See footnote "f"	See footnote "f"
Identification numbers:[h]		
CAS registry	39227-61-7 (1,2,3,4,7-); 40321-76-4 (1,2,3,7,8-); 58802-08-7 (1,2,4,7,8-)[c]	57653-85-7 (1,2,3,6,7,8-)[e]; 64461-98-9 (1,2,3,6,7,9-)[c]; 19408-74-3 (1,2,3,7,8,9-)[e]; 39227-62-8 (1,2,4,6,7,9-)[e]; 34465-46-8[e]
NIOSH RTECS	HP3370000 (1,2,3,4,7-); HP3395000 (1,2,3,7,8-); HP3420000 (1,2,4,7,8-)[c]	HP3280000 (1,2,3,4,7,8-); HP3280100 (1,2,3,6,7,8-); HP3290000 (1,2,3,6,7,9-); HP3310000 (1,2,3,7,8,9-); HP3313000 (1,2,4,6,7,9-)[c]
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	No data	4154 (1,2,3,6,7,8-)[e]; 6867[e]; 6866 (1,2,3,7,8,9-)[e]
NCI	No data	CO3703 (1,2,3,6,7,8-)[e]

Table 3-1. Chemical Identity of CDDs[a] (continued)

Characteristic	Heptachlorodibenzo-p-dioxins	Octachlorodibenzo-p-dioxin
Chemical name	Heptachlorodibenzo-p-dioxin (CAS #37871-00-4)[e]	Octachlorodibenzo-p-dioxin [e]
Synonym(s)	1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin; 1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzo[b,e](1,4) dioxin; 1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzo-dioxin; 1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzo-para-dioxin[c]; Heptachlorodibenzo (b,e)(1,4)dioxin[e]	1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin; OCDD; Octachlorodibenzodioxin; Octachlorodibenzo[b,e](1,4)dioxin; Octachlorodibenzo-p-dioxin; 1,2,3,4,6,7,8,9-Octachlorodibenzodioxin; 1,2,3,4,6,7,8,9-Octachlorodibenzo(b,e)(1,4)dioxin; Octachloro-para-dibenzodioxin[b]
Total number of possible isomers	2	1
Registered trade name(s)	No data	No data
Chemical formula	$C_{12}HCl_7O_2$[c]	$C_{12}Cl_8O_2$[e]
Chemical structure[b,f]	See footnote "f"	See footnote "f"
Identification numbers:[h]		
CAS registry	35822-46-9 (1,2,3,4,6,7,8-)[i]; 58200-70-7 (1,2,3,4,6,7,9-)[c]; 37871-00-4 (b,e)(1,4)[e]	3268-87-9[e]
NIOSH RTECS	HP3190000 (1,2,3,4,6,7,8-)[c];	HP3350000[e]
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	6474 (1,2,3,4,6,7,9-)(b,e)(1,4)[e]	6480[e]
NCI	No data	CO3678[e]

[a] In some cases, information regarding chemical identity was not available for all isomers of a homologous class.
[b] IARC 1977
[c] RTECS 1996
[d] 1,2,7,8- is the same isomer as 2,3,6,7-in tetrachlorodibenzo-p-dioxins
[e] HSDB 1995
[f] The structural formula of unsubstituted dibenzo-para-dioxin and the numbering of the carbon atoms in the ring are given under monochlorodibenzo-p-dioxins. The chlorinated dibenzo-para-dioxins contain chlorine atoms at the positions indicated in their names (IARC 1977).
[g] Chemical identity information for 2,3,7,8-TCDD is shown in bold.
[h] Specific chlorine substitutions are given in parentheses following the identification numbers when multiple identification numbers are given
[i] Aster 1995
[j] Example, alternative nomenclature shown; not all possible isomers are listed but can be extrapolated from the general structure or from the literature (Ryan et al. 1991)

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

Table 3-2. Physical and Chemical Properties of CDDs[a]

Characteristic	Monochlorodibenzo-p-dioxins	Dichlorodibenzo-p-dioxins	Trichlorodibenzo-p-dioxins
Molecular weight	218.6	253.1	287.5
Color	Colorless[b]	Colorless [b,k]	Colorless (1,2,4-)[b]
Physical state	Crystals (1-); solid (2-)[b]	Needles (1,6-); solid (2,3-, 2,8-); crystals (2,7-)[b]	Solid (1,2,4-)[b]
Melting point	105.5 °C (1-); 89.0 °C (2-)[d]	114-115 °C (1,3-); 184-185°C (1,6-)[b]; 164 °C (2,3-); 210 °C (2,7); 151 °C (2,8-)[d]	129°C (1,2,4-)[d]; 128-129°C (1,2,4-)[b]; 153–163°C (2,3,7-)[b]
Boiling point	No data	No data	374 °C [l]
Density: at 25 °C	No data	No data	No data
Odor	No data	No data	No data
Odor threshold: Water Air	No data No data	No data No data	No data No data
Solubility: Water at 25 °C[h]	0.417 mg/L (1-); 0.278–0.318 mg/L (2-)[d]	0.0149 mg/L (2,3-); 0.00375 mg/L (2,7-); 0.0167 mg/L (2,8-)[d]	0.00841 mg/L (1,2,4-)[d]; 4.75×10^{-3} mg/L [l]
Organic solvent(s)[p]	No data	No data	No data
Partition coefficients: Log K_{ow} Log K_{oc}	4.52–5.45 (1-,2-)[f] No data	5.86–6.39 (2,7-)[f] No data	6.86–7.45 (1,2,4-)[f] No data

Table 3-2. Physical and Chemical Properties of CDDs[a] (continued)

Characteristic	Monochlorodibenzo-p-dioxins	Dichlorodibenzo-p-dioxins	Trichlorodibenzo-p-dioxins
Vapor pressure at 25 °C	9.0×10^{-5} mm Hg (1-); 1.3×10^{-4} mm Hg (2-)[e]	2.9×10^{-6} mm Hg (2,3-); 9.0×10^{-7} mm Hg (2,7-); 1.1×10^{-6} mm Hg (2,8-)[e]	2.7×10^{-7} mm Hg (1,3,7-); 7.5×10^{-7} mm Hg (1,2,4-)[e]; 6.46×10^{-8} mm Hg[l]
Henry's law constant at 25 °C	82.7×10^{-6} to 146.26×10^{-6} atm·m^3/mol[d]	21.02×10^{-6} to 80.04×10^{-6} atm·m^3/mol (2,3-, 2,7-, 2,8-)[d]	37.9×10^{-6} atm·m^3/mol (1,2,4-)[d]
Degradation	atmospheric lifetime using gas-phase reaction with OH radical = 0.5 days[q]	atmospheric lifetime using gas-phase reaction with OH radical = 0.5 to 0.7 days[q]	atmospheric lifetime using gas-phase reaction with OH radical = 0.7 to 0.9 days[q]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors in air at 25 °C, 760 mm Hg	1 mg/m^3 = 0.112 ppm; 1 ppm = 8.94 mg/m^3	1 mg/m^3 = 0.0966 ppm; 1 ppm = 10.35 mg/m^3	1 mg/m^3 = 0.0850 ppm; 1 ppm = 11.76 mg/m^3
Explosive limits	No data	No data	No data

Table 3-2. Physical and Chemical Properties of CDDs[a] (continued)

Characteristic	Tetrachlorodibenzo-p-dioxins [n]	Pentachlorodibenzo-p-dioxins	Hexachlorodibenzo-p-dioxins
Molecular weight	322	356.4	390.9
Color	White or colorless[b,c] (2,3,7,8-); colorless needles (2,3,7,8-)[k]; colorless (1,2,3,4-, 1,3,6,8-)[b]	Colorless (1,2,3,4,7-)[b]	Colorless (1,2,3,4,7,8-, 1,2,4,6,7,9-)[b]
Physical state	Crystalline solid[c] (2,3,7,8-)	Solid (1,2,3,4,7-)[b]	Solid (1,2,3,4,7,8-, 1,2,4,6,7,9-)[b]
Melting point	190 °C (1,2,3,4-); 175 °C (1,2,3,7-)[d]; 219-219.5 °C (1,3,6,8-); 193.5-195 °C (1,3,7,8-); 305-306 °C (2,3,7,8-)[b]	195-196°C (1,2,3,4,7-); 240-241°C (1,2,3,7,8-); 205-206°C (1,2,4,7,8-)[b]	273 °C (1,2,3,4,7,8-)[d]; 275 °C (1,2,3,4,7,8-)[b]; 285-286 °C (1,2,3,6,7,8-); 243-244 °C (1,2,3,7,8,9-); 238-240 °C (1,2,4,6,7,9-)[b]
Boiling point	446.5 °C[f] (2,3,7,8-)	No data	No data
Density: at 25 °C	1.827 g/mL[g] (2,3,7,8-)	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 25 °C	4.7×10^{-4}-6.3×10^{-4} mg/L (1,2,3,4-)[d,i] 4.2×10^{-4} mg/L (20°C) (1,2,3,7-); 3.2×10^{-4} mg/L (20°C) (1,3,6,8-); 1.9×10^{-5} mg/L (2,3,7,8)[r] 7.9×10^{-6}-3.2×10^{-4} mg/L (2,3,7,8-)[d]	1.18×10^{-4} mg/L (20°C) (1,2,3,4,7-)[d]	4.42×10^{-6} mg/L (20°C) (1,2,3,4,7,8-)[d]
Organic solvent(s)[p]	o-dichlorobenzene, chlorobenzene, benzene, chloroform, n-octanol[b]	No data	No data
Partition coefficients:			
Log K_{ow}	7.02–8.7 (1,2,3,7-)[f,e]; 7.02 (2,3,7,8-)[d]; 7.39–7.58 (2,3,7,8-)[j]; 6.8 (2,3,7,8-TCDD)[m]; 6.6 (1,2,3,4-TCDD)[m]	8.64–9.48 (1,2,3,4,7-)[d]	9.19–10.4 (1,2,3,4,7,8-)[f]
Log K_{oc}	No data	No data	No data

Table 3-2. Physical and Chemical Properties of CDDs[a] (continued)

Characteristic	Tetrachlorodibenzo-p-dioxins[n]	Pentachlorodibenzo-p-dioxins	Hexachlorodibenzo-p-dioxins
Vapor pressure at 25 °C	$7.5x10^{-9}$ mm Hg (1,2,3,7-)[d]; $4.8x10^{-8}$ mm Hg (1,2,3,4-)[e]; $1.5x10^{-9}$-$3.4x10^{-5}$ mm Hg (2,3,7,8-)[e]; $5.3x10^{-9}$-$4.0x10^{-3}$ mm Hg (1,3,6,8-)[d]; $7.4x10^{-10}$ mm Hg (2,3,7,8-)[k]	$6.6x10^{-10}$ mm Hg (1,2,3,4,7-)[d]	$3.8x10^{-11}$ mm Hg (1,2,3,4,7,8-)[d]
Henry's law constant at 25 °C	$16.1x10^{-6}$–$101.7x10^{-6}$ atm·m^3/mol (2,3,7,8-); $7.01x10^{-6}$–$101.7x10^{-6}$ atm·m^3/mol[d]	$2.6x10^{-6}$ atm·m^3/mol (1,2,3,4,7-)[d]	$44.6x10^{-6}$ atm·m^3/mol (1,2,3,4,7,8-)[d]
Degradation	photodegradation half-life on grass (2,3,7,8-)=44 h(k_2 = 0.0156 h^{-1})[m,o]; atmospheric lifetime using gas-phase reaction with OH radical = 0.8 to 2 days[q]	atmospheric lifetime using gas-phase reaction with OH radical = 1.1 to 2.4 days[q]	atmospheric lifetime using gas-phase reaction with OH radical = 1.5 to 3.4 days[q]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors in air at 25 °C, 760 mm Hg	1 mg/m^3 = 0.0759 ppm 1 ppm = 13.17 mg/m^3	1 mg/m^3 = 0.0686 ppm 1 ppm = 14.58 mg/m^3	1 mg/m^3 = 0.0625 ppm 1 ppm = 15.99 mg/m^3
Explosive limits	No data	No data	No data

Table 3-2. Physical and Chemical Properties of CDDs[a] (continued)

Characteristic	Heptachlorodibenzo-p-dioxins	Octachlodibenzo-p-dioxin
Molecular weight	425.3	459.8
Color	No data	No data
Physical state	No data	No data
Melting point	265 °C (1,2,3,4,6,7,8-)[d]	332 °C[d]; 330 °C [k]
Boiling point	507.2 °C[e]	510 °C[e]; 485 °C [m]
Density: at 25 °C	No data	No data
Odor	No data	No data
Odor threshold: Water Air	No data No data	No data No data
Solubility: Water at 25 °C	2.4×10^{-6} mg/L at 20°C (1,2,3,4,6,7,8-)[d] ; 1.9×10^{-3} mg/L at 20°C (b,e)(1,4) [k]	7.4×10^{-8} mg/L[d] ; $0.4 \pm 0.1 \times 10^{-9}$ g/L at 20 °C[k]; 2.27×10^{-9} mg/L [m]
Organic solvent(s)[p]	No data	Acetic acid, anisole, chloroform, o-dichlorobenzene, dioxane, diphenyl oxide, pyridine, xylene[b]
Partition coefficients: Log K_{ow}	9.69–11.38 (1,2,3,4,6,7,8-)[f]	10.07–12.26[f] ; 8.78-13.37 [k]
Log K_{oc}	No data	No data
Vapor pressure at 25 °C	5.6×10^{-12} mm Hg; (1,2,3,4,6,7,8-)[e]; 7.4×10^{-8} mm Hg (b,e)(1,4)[k]	8.25×10^{-13} mm Hg[e]; 1.68×10^{-12} [m]
Henry's law constant at 25 °C	1.31×10^{-6} atm·m^3/mol (1,2,3,4,6,7,8-)[d]; 2.18×10^{-5} atm·m3/mol [k]	6.74×10^{-6} atm·m^3/mol[d,k]

Table 3-2. Physical and Chemical Properties of CDDs[a] (continued)

Characteristic	Heptachlorodibenzo-p-dioxins	Octachlodibenzo-p-dioxin
Degradation	Atmospheric lifetime using gas-phase reaction with OH radical = 4.4 days[q]	Atmospheric lifetime using gas-phase reaction with OH radical = 9.6 days[q]
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors in air at 25 °C, 760 mm Hg	1 mg/m^3 = 0.0575 ppm 1 ppm = 17.39 mg/m^3	1 mg/m^3 = 0.0532 ppm 1 ppm = 18.81 mg/m^3
Explosive limits	No data	No data

[a] In some cases, information regarding chemical and physical properties was not available for all isomers of a homologous class
[b] IARC 1977
[c] Sax and Lewis 1987
[d] Shiu et al. 1988
[e] Rordorf 1989
[f] Webster et al. 1985
[g] Schroy et al. 1985
[h] Solubility is given for 25 °C unless noted otherwise in text.
[i] Doucette and Andren 1988
[j] Des Rosiers 1986
[k] HSDB 1995
[l] ASTER 1995
[m] McCrady and Maggard 1993
[n] Physical & chemical properties of 2,3,7,8-TCDD are shown in bold
[o] k_2 = elimination rate constants
[p] In most cases no specific solubilities were found. However, solvation in organic solvents such as toluene, hexane and methylene chloride is possible given that these solvents are used in extraction and analysis methods (see Chapter 6).
[q] Atkinson 1991
[r] Marple et al. 1986b

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

4.1 PRODUCTION

CDDs are not manufactured commercially in the United States except on a small scale for use in chemical and toxicological research. CDDs are unique among the large number of organochlorine compounds of environmental interest in that they were never intentionally produced as desired commercial end products (Zook and Rappe 1994). Typically, CDDs are unintentionally produced during various uncontrolled chemical reactions involving the use of chlorine (EPA 1990c) and during various combustion and incineration processes (Zook and Rappe 1994). In the process of making white paper products, for example, chlorine or chlorine derivatives are often used as the primary bleaching agent. As a result, several chlorinated organic compounds are formed, including small amounts of CDDs (EPA 1990c). These chlorinated compounds not only leave the mills in the pulp and paper products, they are also released through waste waters (effluents from the mills) and sludge produced as a result of waste water treatment (EPA 1990c). CDDs are also produced as undesired by-products during the manufacture of chlorinated phenols such as pentachlorophenol, 2,4,5-trichlorophenol, and related chemicals, and during incineration of chlorinated wastes (IARC 1977; NTP 1989; Podoll et al. 1986). By far the greatest unintentional production of CDDs occurs via various combustion and incineration processes including all forms of waste incineration (municipal, industrial, and medical), many types of metal production (iron, steel, magnesium, nickel, lead, and aluminum), and fossil fuel and wood combustion (Czuczwa and Hites 1986a, 1986b; Oehme et al. 1987, 1989; Zook and Rappe 1994). More extensive information on sources of CDDs released to the environment can be found in Chapter 5.

In general, there are two conventional methods for the preparation of CDDs for research purposes: condensation of a polychlorophenol and direct halogenation of the parent dibenzo-*p*-dioxin or a monochloro-derivative. For example, 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) is generally synthesized by the condensation of two molecules of 2,4,5-trichlorophenol in the presence of a base at high temperatures or by chlorination of dibenzo-p-dioxin in chloroform in the presence of iodine and ferric chloride (EPA 1987k; IARC 1977). Other methods of 2,3,7,8-TCDD synthesis include the following: pyrolysis of sodium α-(2,4,5-trichlorophenoxy) propionate at 500 EC for 5 hours; reaction of dichlorocatechol salts with *o*-chlorobenzene by refluxing in alkaline dimethyl sulfoxide; ultraviolet irradiation of CDDs of high chlorine content; Ullman reaction of chlorinated phenolates at 180–400 EC;

pyrolysis of chlorinated phenolates and chlorinated phenols; and heating 1,2,4-trichloro-5-nitrobenzene and 4,5-dichlorocatechol in the presence of a base (EPA 1984a; IARC 1977).

1,2,3,4-TCDD has been prepared by refluxing a mixture of catechol, potassium carbonate, pentachloronitro-benzene and acetone in nitrogen (IARC 1977).

DCDD can be synthesized by two methods. In the first method, 2-bromo-4-chlorophenol and potassium hydroxide are dissolved in methanol and evaporated to dryness. The residue is then mixed with bis(2-ethoxyethyl) ether, ethylene diacetate, and a copper catalyst; and then heated, cooled, and eluted from a chromatographic column with chloroform. This residue is evaporated and then sublimed. DCDD can also be synthesized by heating the potassium salt of 2,4-dichlorophenol in the presence of copper powder in a vacuum sublimation apparatus (IARC 1977).

1,2,4,6,7,9-HxCDD has been made by heating the potassium salt of 2,3,5,6-tetrachlorophenol with powdered copper and potassium carbonate in a vacuum sublimation apparatus (IARC 1977).
1,2,3,4,7,8-HxCDD has been prepared by mixing 1,2,3,4-TCDD, ferric chloride, chloroform, and a crystal of iodine and then adding a solution of chlorine in carbon tetrachloride (IARC 1977).

OCDD has been synthesized by the following methods: irradiation of aqueous solutions of CDD-free sodium pentachlorophenol with ultraviolet light; heating the potassium salt of pentachlorophenol; heating pentachlorophenol in the presence of an initiator, such as chlorine, bromine, iodine, or 2,3,4,4,5,6-hexa-chloro-2,5-cyclohexadienone; and heating hexachlorocyclohexadienone in an atmosphere of carbon dioxide for 30 minutes (Crosby and Wong 1976; EPA 1984a; IARC 1977).

At present, the only reported producers of CDDs are Eagle Picher Industries, Inc., located in Lenexa, Kansas, and Cambridge Isotope Laboratories, located in Andover, Massachusetts. Eagle Picher Industries produces 2,3,7,8-TCDD and OCDD for research purposes (SRI 1991). Cambridge Isotope Laboratories produced unlabeled chlorodioxin standards (TCDD through HpCDD) and C^{13} labeled chlorodioxin standards (DCDD through OCDD) for use in chemical analyses and in toxicological research (Cambridge Isotope Laboratories 1995).

Since CDD releases are not required to be reported under Superfund Amendments and Reauthorization Act (SARA) Section 313, there are no data on CDDs in the 1994 Toxics Release Inventory (TRI) (EPA 1995g).

4.2 IMPORT/EXPORT

2,3,7,8-TCDD is not imported into the United States (NTP 1989). There were no data located pertaining to the export of 2,3,7,8-TCDD or any other CDD for research purposes.

4.3 USE

The only reported use of CDDs/CDFs is as research chemicals (NTP 1989). A large diversified group of researchers use various CDDs in studies of toxicology, environmental fate, transformation, and transport, and in residue analysis of a variety of contaminated media. CDDs have been tested for use in flame-proofing polymers such as polyesters and against insects and wood-destroying fungi; however, there are no data reporting its commercial production or use for these purposes (IARC 1977).

4.4 DISPOSAL

The 1994 estimates on the degree of TCDD contamination in the environment indicated that approximately 500,000 tons of soil and sediment in the United States were contaminated with 2,3,7,8-TCDD (Hilarides et al. 1994). The development of treatment technologies for CDD-contaminated soils and wastes needed to address unique problems associated with CDDs: for example, they are insoluble in water, only slightly soluble in organic solvents, have a strong affinity for adsorption on organic matter, and are biologically and environmentally stable (U.S. Congress 1991). In order to meet the clean-up standards established for CDDs, the treatment system must be capable of removing the CDDs from the contaminated matrix (U.S. Congress 1991). Several treatment or disposal methods for CDDs and CDD-contaminated materials have been investigated, including land disposal, thermal destruction, and chemical and biological degradation. Each of these methods has limitations regarding economics, technical feasibility, and acceptability (HSDB 1995).

Land disposal of CDD-containing wastes is currently prohibited (EPA 1986f, 1988f). The Toxic Substances Control Act (TSCA) regulates the use, disposal, and distribution in commerce of process waste water treatment sludges intended for land application from pulp and paper mills employing chlorine or

chlorine derivative-based bleaching processes (EPA 1991b, 1991c). Also, under the Marine Protection Research and Sanctuaries Act, ocean dumping of CDD-containing wastes is prohibited except when only trace amounts are present (EPA 1977a, 1977b).

Thermal destruction technologies offer the most straightforward approach to treating or disposing of CDD-contaminated materials because under the appropriate conditions the breakdown of the CDDs is assured (U.S. Congress 1991). The thermal treatment technologies that are currently used to treat waste containing hazardous or toxic constituents and that have demonstrated potential use toward the treatment of CDD-contaminated waste include rotary kiln incineration, liquid injection incineration, fluidized-bed incineration, advanced electric reactor (AER), infrared incineration, plasma arc pyrolysis incineration, supercritical water oxidation, and *in situ* vitrification (U.S. Congress 1991). In addition to kiln incinerators, the technologies that have been field-tested for treating CDD-contaminated media under EPA's Superfund Innovative Technology Evaluation (SITE) program include dechlorination, stabilization, and *in situ* vitrification (U.S. Congress 1991). Although some alternatives look promising and have been shown effective in the laboratory or in application to other pollutants, more development and testing is needed to demonstrate viability for large-scale treatment of CDD contamination.

Incineration, involving the high-temperature oxidation of CDD molecules, is the most extensively tested method for disposal of CDDs. CDDs such as TCDD, PeCDD, and HxCDD are classified by EPA as Principal Organic Hazardous Constituents (POHCs) and are required to be incinerated under conditions that achieve a destruction and removal efficiency of 99.99% (EPA 1990b; Sedman and Esparza 1991). Incinerator operating conditions currently considered adequate for destruction of 2,3,7,8-TCDD and most other chlorinated organics require a temperature of at least 1,500–2,600 EF, with residence times of at least 30 minutes (although 1.5 hours is a more common residence time) to ensure complete destruction (EPA 1990a). Thermal destruction of CDDs that are adsorbed on fly ash can be accomplished through the use of a rotary kiln furnace combined with a baghouse filter for the recycling of entrained fly ash and an activated carbon filter for adsorption of CDD traces transported in the gas phase. This method is capable of destroying 99.5% of CDDs in fly ash, which is considered a high level of efficiency (Kahr et al. 1990). EPA's Mobile Incineration System, a transportable rotary kiln system, was judged to be more than adequate for detoxifying CDD-contaminated solids and liquids after it was performance-tested with a variety of uncontaminated soils and other solid wastes, and thus could be expected to accomplish a successful CDD trial burn. The system, which has been extensively modified for field use, consists of a

rotary-kiln, a secondary combustion chamber, an air pollution control unit, and separate continuous stack-gas analysis capabilities (HSDB 1995). In 1977, the U.S. Air Force disposed of Agent Orange contaminated with 2,3,7,8-TCDD by high temperature incineration at sea (Bumb et al. 1980). The high flame temperature reached 1,500 EC in the incinerator, and EPA determined a combustion efficiency of 99.9% for 2,3,7,8-TCDD.

Kiln incinerators have been used to treat a variety of containerized and noncontainerized solid and liquid wastes. Since the waste can be treated individually or simultaneously, the versatility of this technology has made it popular in the United States for disposing of hazardous waste. For the disposal of CDD-containing waste, however, kiln incineration is more commonly practiced in Europe than in the United States (U.S. Congress 1991). Although liquid injection incineration has been used for ocean-based incineration of Agent Orange, certain limitations must be considered before applying the technology to treating CDD contamination. These limitations include the applicability of the technology only to combustible low-viscosity liquids and slurries that can be pumped; atomizing the waste prior to injection into the combustor; and the importance of particle size because burners are susceptible to clogging (U.S. Congress 1991). Fluidized-bed combustion (FBC) systems have traditionally been used to treat the sludge produced by municipal waste treatment plants and waste generated from oil refineries, pulp and paper mills, and the pharmaceutical industry. The system consists of a vertical refractory-lined vessel which holds a perforated plate. A bed of granular material, usually sand, is placed on the perforated plate. The system uses forced hot air to fluidized the bed and cause a highly turbulent zone that ensures the mixing of the waste with bed particles and the combustion air. Combustion is facilitated by an overhead burner (U.S. Congress 1991). The type and size of materials to be treated are critical because variations in gravity and density could be deleterious to the process (U.S. Congress 1991). Modification of the traditional FBC system for treatment of chlorinated wastes continues to be investigated by researchers in the private sector. A modified system designed by Waste-Tech Services, Inc. uses a granular bed composed of a mixture of combustion catalyst and limestone. The results of the trial burn for the Waste-Tech Services system which used chlorinated waste containing carbon tetrachloride, tetrachloroethane, p-dichlorobenzene and some CDDs and CDFs, showed no measurable amount of any of the chlorinated pollutants treated and no 2,3,7,8-TCDD in any of the samples tested (U.S. Congress 1991). *In situ* vitrification (ISV), which treats waste in place, solidifies all materials not volatilized or destroyed. Bench-scale testing of ISV on soils containing 10 ppb CDDs showed destruction removal efficiency (DRE) values of 99.9999% (U.S. Congress 1991).

Since the early 1970s, several chemical methods have been investigated for the degradation of CDDs. Treatment of CDD-contaminated materials with alkali polyethylene glycolate (APEG) reagents at hazardous waste sites has been demonstrated to successfully destroy CDDs in liquid wastes and to be viable even under difficult circumstances. This method involves the reaction of potassium hydroxide with polyethylene glycol to form an alkoxide that reacts with one of the chlorine atoms on the CDD to produce an ether and potassium chloride. Bioassays indicate that the by-products produced by treating 2,3,7,8-TCDD with APEG reagents do not bioaccumulate or bioconcentrate, do not cause mutagenicity, and are far less toxic than 2,3,7,8-TCDD (Klee 1988). Cleavage of the ether linkages with the formation of halophenols may be achieved by treatment with strong acids or quaternary ammonium salts, but the dibenzodioxin nucleus is resistant to chemical attack. Oku et al. (1995) investigated the dechlorination of polychlorinated dibenzo-p-dioxins (CDDs) and polychlorinated dibenzofurans (CDFs) using a modified alkali-metal hydroxide method. The destruction reagent, prepared by dissolving either potassium hydroxide or sodium hydroxide in 1,3-dimethyl-2-imidazolidinone (DMI) destroyed all components regardless of the difference in the number of chlorine atoms or isomers of CDDs and CDFs (Oku et al. 1995). The efficiency of the methods was evaluated under varying conditions; in the presence and absence of water, at 90 and 50 EC, for 0.5 and 5 hours. Although the degree of CDD destruction (99.95–99.80%) was less than that for CDFs (99.99–99.98%), overall, the investigators considered the DMI reagent to be more useful than the polyethylene glycols because of its stability under strongly basic conditions and its efficiency in the presence of water (Oku et al. 1995).

Ruthenium tetroxide treatment can cause oxidative degradation of CDDs. This method can be used for detoxification of glassware and artifacts, or for the periodic purging of industrial reactors to counteract the accumulation of CDD residues (HSDB 1995). There is no available evidence on the nature of fragments formed during oxidation of the CDDs; however, the related chlorophenols undergo extensive decomposition to yield chlorine ions and no significant levels of organic products (HSDB 1995). Other chemical methods of detoxification include exposure to ultraviolet light or gamma radiation, the use of ozone or special chloroiodide compounds, and the use of solvents or adsorbents to concentrate CDDs into smaller volumes for final disposal by incineration (HSDB 1995).

Dougherty et al. (1993) conducted a theoretical analysis of a proposed *in situ* method for decontaminating soil by photodegradation. Up to 86% of TCDD in the soil can be degraded by this process (Zhong et al. 1993). Because of its extremely low water solubility and volatility, TCDD is a very persistent soil contaminant. With the method, based on the physical properties that facilitate photolysis of TCDD by

sunlight, an organic solvent mixture (2:1 w/w) of tetradecane and 1-butanol is applied to the contaminated soil (Dougherty et al. 1993). The controlling factors in TCDD photodegradation are desorption of the compound from the soil, the transport mechanism to the soil surface, and the availability of sunlight. As the solvents remove the tightly bound TCDD from the soil, convective upward movements of the compound are caused by the evaporation of the solvent (Dougherty et al. 1993; Zhong et al. 1993). The effectiveness of the process also depends on a balance between the convective movement and sunlight availability for degradation (Dougherty et al. 1993). Modeling conducted by Zhong et al. (1993) identified and quantified the controlling factors governing the TCDD photodegradation process. Following the concentration variation of TCDD in the top 2 mm of soil through sunlight/night cycles over an exposure period of 15 days, the model showed that during the daytime of the first few days, there is little accumulation of TCDD as the losses due to photodegradation were almost equal to the convective flux in magnitude but with different signs. Although the losses due to photodegradation drop to zero at night, the convective flux effected a build-up of TCDD. The losses due to photodegradation held steady while the convective movements decreased as evaporation slowed down (Zhong et al. 1993). A balance between the build-up of TCDD concentration at night and the drop in concentration during the day did not occur until the eleventh day of exposure (Zhong et al. 1993).

Hilarides et al. (1994) investigated degradation of TCDD in the presence of surfactants. Their results indicated that radiolytic destruction of TCDD using γ radiation can be achieved. Greater than 92% of the TCDD was destroyed in soils amended with 100 ppb TCDD, 25% water, and 2% nonionic surfactant using ^{60}Co at high radiation doses (800 kGy or 80 Mrad). The use of ^{60}Co as a source avoids the temperature increases and power requirements of other sources of ionizing radiation such as an electron beam. It is also better suited for soil application because of its greater penetration depths (Hilarides et al. 1994).

Biotreatment systems which use microorganisms for degradation of refractory organopollutants, like CDDs, are also being considered. *Phanerochaete chrysosporium*, a white rot fungus, has shown the ability to slowly degrade 2,3,7,8-TCDD in the laboratory (Bumpus et al. 1985; Des Rosiers 1986). The ability of this fungus to metabolize 2,3,7,8-TCDD is thought to be related to its extracellular lignin degrading enzyme system (Bumpus et al. 1985; Des Rosier 1986).

Other proposed methods of disposal are burial in salt mines and inclusion of these chemicals with nuclear fission by-products in secured cavities (HSDB 1995).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chlorinated dioxins (CDDs) are a family of compounds that includes some extremely toxic and potent congeners. The two most toxic of the CDDs in mammals are 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD (Buser 1987; Poland and Knutson 1982; Safe 1986; WHO 1997). In general, the more toxic congeners to mammals appear to be the 2,3,7,8-substituted tetra-, penta-, and hexachloro- compounds, (e.g., 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD) (Poland and Knutson 1982; Safe 1986; WHO 1997). A more detailed discussion of the relative toxicities of the different CDD congeners is given in Section 2.5, Relevance to Public Health.

CDDs usually occur in the environment concurrently with other chemicals such as chlorinated dibenzofurans (CDFs). CDDs and CDFs are highly persistent compounds and have been detected in air, water, soil, sediments, animals, and foods. CDFs include 135 congeners, which are structurally similar to CDDs and which elicit a number of similar toxicological and biochemical responses in animals (for more information on CDFs see ATSDR 1994). CDDs and CDFs are released to the environment during combustion processes (e.g., municipal solid waste, medical waste, and industrial hazardous waste incineration, and fossil fuel and wood combustion); during the production, use, and disposal of certain chemicals (e.g., PCBs, chlorinated benzenes, chlorinated pesticides); during the production of bleached pulp by pulp and paper mills; and during the production and recycling of several metals (Buser et al. 1985; Czuczwa and Hites 1986a, 1986b; Oehme et al. 1987, 1989; Zook and Rappe 1994). The EPA has developed procedures for estimating risks associated with exposures to mixtures of CDDs and CDFs in environmental matrices (EPA 1989e). This approach is based on the assignment of 2,3,7,8-TCDD toxic equivalence factors (TEFs) to CDD/CDF congeners or homologues in complex mixtures. The rationale behind the use of TEFs is explained in Section 2.5, Relevance to Public Health. **Although the focus of this profile is CDDs, it should be recognized that most exposure scenarios involve exposure to CDDs, CDFs, and the non-ortho polychlorinated biphenyls (PCBs) that have CDD-like toxicity; many of these exposure scenarios are discussed in this chapter.** These exposures are usually reported in TEQs (for more information see Section 2.5, Relevance to Public Health, Toxic Equivalency Factors [TEFs] and Toxic Equivalents [TEQs]). Over the past several years sets of TEFs have been

developed, varying slightly from one to another. The reader is encouraged to consult the original literature for specific details on TEQs computation.

CDDs (TCDD, PeCDD, HxCDD, HpCDD, OCDD) are ubiquitous in the environment (Podoll et al. 1986). Although all of the sources or processes that contribute to CDDs in the environment have not been identified, CDDs are known to be formed in the manufacture of chlorinated intermediates and pesticides, during smelting of metals (EPA 1998j), in the incineration of municipal, medical, and industrial wastes (Podoll et al. 1986), and from the production of bleached wood pulp and paper (Fletcher and McKay 1993). CDDs are also found in emissions from the combustion of various other sources, including coal-fired or oil-fired power plants, wood burning, and home heating systems (Chiu et al. 1983; Czuczwa and Hites 1984; EPA 1998j; Gizzi et al. 1982; Thoma 1988). Generally, the more highly chlorinated CDDs are the most abundant congeners present in the emissions from these combustion sources. CDDs also occur in other combustion products (e.g., cigarette smoke) (Bumb et al. 1980; Lofroth and Zebuhr 1992; Muto and Takizawa 1989), automobile exhaust from cars running on leaded gasoline with chlorine scavengers and to a lesser extent from cars running on unleaded gasoline (Bingham et al. 1989; Marklund et al. 1987, 1990), and diesel exhaust (Jones 1995; Cirnies-Ross et al. 1996). CDDs/CDFs can form during the synthesis and combustion of chlorine-containing materials, such as polyvinylchloride (PVC), in the presence of naturally occurring phenols, vegetation treated with phenoxy acetic acid herbicides, paper and wood treated with chlorophenols, and pesticide-treated wastes (Arthur and Frea 1989).

CDDs occur as contaminants in the manufacture of various pesticides and, as a result, have been released to the environment during use of these pesticides. 2,3,7,8-TCDD is a by-product formed in the manufacture of 2,4,5-trichlorophenol (2,4,5-TCP) (Arthur and Frea 1989). 2,4,5-TCP was used to produce the bactericide, hexachlorophene, and the chlorophenoxyherbicide, 2,4,5-trichlorophenoxy acid (2,4,5-T). Trichlorophenol-based herbicides have been used extensively for weed control on crops, rangelands, roadways, right-of-ways, etc. Various formulations of 2,4-dichlorophenoxy acetic acid (2,4-D) contaminated mainly with higher chlorinated CDDs/CDFs and 2,4,5-T contaminated mainly with 2,3,7,8-TCDD were used extensively for defoliation and crop destruction by the American military during the Vietnam War. Although six herbicides were used (Orange, Purple, Pink, Green, White, and Blue), herbicide Orange (Agent Orange) was the primary defoliant (Wolf et al. 1985). Hexachlorophene use has been restricted by the FDA and its disposal is regulated by EPA under the Resource Conservation and Recovery Act (RCRA). In 1983, EPA canceled registration for all chlorophenoxy herbicides used on foods, rice paddies, pastures, and rangelands (IARC 1986b). 2,4,5-T can no longer be used legally in the

United States for any purpose (IARC 1986b). Other countries, including Canada, Sweden, the Netherlands, Australia, Italy, and the Federal Republic of Germany, have also canceled registrations for 2,4,5-T (IARC 1986b), but many other countries have not. Currently, 2,4,5-T can be produced with lower 2,3,7,8-TCDD concentrations than were previously possible. 2,4,5-TCP production has been discontinued in many countries, including the United States, Canada, the United Kingdom, the Federal Republic of Germany, and Austria (IARC 1986a). HxCDD, HpCDD, and OCDD are known contaminants of pentachlorophenol (PCP), primarily a wood preservative and pesticide, which was used extensively in the 1970s and is still used today (to a lesser extent) in the lumber industry. PCP is currently registered as a restricted-use pesticide in the United States (Sine 1990).

Although little definitive data exist to prove or disprove that CDDs form during natural processes, results from dated sediment cores have shown that there were significant increases in CDDs and CDFs after about 1940 (Czuczwa and Hites 1984, 1986b, 1986b) and lower levels of CDDs are currently found in persons from less industrialized countries (Schecter et al.1991a). The congener/homologue profile of the sediments was similar to that of atmospheric samples, strongly suggesting that combustion processes were the source of CDDs in the sediments. The historical increase in CDDs/CDFs also was similar to the trends for the production, use, and disposal of chlorinated organics, suggesting that accumulation of these compounds in the environment is a recent phenomenon related to the production, use, and subsequent incineration of chlorinated organic chemicals (Schecter et al. 1988).

CDDs are ubiquitous in the environment and are found at low background levels (parts per trillion [ppt] or parts per quadrillion [ppq]) in the air, water, and soil. Lower levels are found in biological and environmental samples from less industrialized rural regions than in those from more industrialized urban regions (Czuczwa and Hites 1986a; Des Rosiers 1987; Edgerton et al. 1989; Schecter et al. 1989e, 1989g, 1991a, 1994d; Tiernan et al. 1989b). HpCDD and OCDD are the most common CDDs found in environmental samples (Christmann et al. 1989b; Clement et al. 1985, 1989; Pereira et al. 1985; Reed et al. 1990; Tashiro et al. 1989a; Tiernan et al. 1989b).

The environmental fate and transport of CDDs involve volatilization, long-range transport, wet and dry deposition, photolysis, bioaccumulation, and biodegradation (Kieatiwong et al. 1990). CDDs strongly partition to soils and sediments. Due to their low vapor pressure and low aqueous solubility and their strong sorption to particulates, CDDs are generally immobile in soils and sediments. Although most biological and nonbiological transformation processes are slow, photolysis has been shown to be relatively

rapid. Photolysis is probably the most important transformation process in environmental systems into which sunlight can penetrate (Kieatiwong et al. 1990). Estimates of the half-life of 2,3,7,8-TCDD on the soil surface range from 9 to 15 years, whereas the half-life in subsurface soil may range from 25 to 100 years (Paustenbach et al. 1992). CDDs have been shown to bioaccumulate in both aquatic and terrestrial biota. CDDs have a high affinity for lipids and, thus, will bioaccumulate to a greater extent in organisms with a high fat content.

Over the past decade, typical concentrations of CDDs in urban air in the United States have averaged 2.3 pg/m^3, with OCDD and HpCDD homologues predominating and 2,3,7,8-TCDD being the least common congener (Smith et al. 1992). CDD concentrations range as follows: OCDD, 0.44–3.16 pg/m^3; HpCDD, 0.21–4.4 pg/m^3; HxCDD, 0.6–0.63 pg/m^3; PeCDD, not detected to 0.1 pg/m^3; and 2,3,7,8-TCDD, <0.04–0.18 pg/m^3 (Edgerton et al. 1989; Eitzer and Hites 1989a, 1989b; Hunt and Maisel 1992; Smith et al. 1992). Although 2,3,7,8-TCDD has been detected in some urban air, it is rarely detected in rural areas (Reed et al. 1990). Ambient air concentrations of 2,3,7,8-TCDD detected in the vicinity of a Superfund clean-up site were on the order of 1 pg/m^3 (Fairless et al. 1987). CDDs have been detected almost exclusively in raw surface waters, rather than in finished drinking water (Jobb et al. 1990). This is not unexpected because CDDs are hydrophobic, and the compounds tend to be adsorbed onto particulate matter in the water column. Conventional water treatment processes appear to be effective in removing the CDDs along with the particulates (Jobb et al. 1990; Meyer et al. 1989). OCDD is the congener most often detected in water supplies at concentrations ranging from 9 to 175 ppq (raw water) and from 19 to 46 ppq (finished water). 2,3,7,8-TCDD concentrations have not been detected in finished drinking water, but were detected in one raw sample at a concentration of 1.7 ppq (Meyer et al. 1989). Concentrations of 2,3,7,8-TCDD in most soils are <12 ppt (Des Rosiers 1987; Nestrick et al. 1986); however, levels in contaminated soils can be several orders of magnitude higher (1,750 ppb) (Tiernan et al. 1985). 2,3,7,8-TCDD and other CDDs, have also been detected in measurable amounts in the sediments of industrialized waterbodies throughout the United States (Bopp et al. 1991; Wenning and Erickson 1994; Wenning et al. 1992, 1993a, 1993b).

In the National Study of Chemical Residues in Fish conducted by the EPA between 1986 and 1989, four CDDs (2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD) were detected at over 50% (54 to 89%) of 388 sites surveyed nationwide (EPA 1992). The most frequently detected CDD compound (1,2,3,4,6,7,8,-HpCDD) was found in fish tissues at 89% of the sites. This compound was also detected at the highest concentrations of 249 ppt (mean 10.52 ppt) wet weight. 2,3,7,8-TCDD

and 1,2,3,7,8-PeCDD, the CDDs currently believed to be most toxic to vertebrates (WHO 1997), were found in fish tissue at 70% and 54% of the sites, respectively. 2,3,7,8-TCDD was found at a mean concentration of 6.9 ppt and a maximum concentration of 204 ppt, and 1,2,3,7,8-PeCDD was found at a mean concentration of 2.38 ppt and a maximum concentration of 54 ppt. With respect to source categories, fish collected near pulp and paper mills using chlorine had the highest median 2,3,7,8-TCDD concentration (5.66 ppt), compared to the second highest median 2,3,7,8-TCDD concentrations of 1.82 ppt at refinery/other industrial sites, and the third highest median 2,3,7,8- TCDD concentration of 1.27 ppt at Superfund sites. Similarly, with respect to source categories, fish collected near pulp and paper mills using chlorine had the highest median 1,2,3,7,8-PeCDD concentration (1.52 ppt), compared to the second highest median concentrations of 1.35 ppt at refinery/other industrial sites, and the third highest median concentration of 1.09 ppt at industrial/urban sites.

The detection of CDDs in blood, adipose tissue, breast milk, and other tissue samples from the general population indicates universal exposure to CDDs from environmental sources (Fürst et al. 1994; Orban et al. 1994; Patterson et al. 1986a; Ryan et al. 1986, 1993a; Schecter and Gasiewicz 1987a, 1987b; Schecter et al. 1986b, 1989e; Stanley 1986; Stanley et al. 1986). The general population is exposed to CDDs released from industrial and municipal incineration processes; exhausts from automobiles using leaded gasoline; cigarette smoke; and foods, including human milk (Pohl and Hibbs 1996; Schecter et al. 1994e). The major source (>90%) of exposure for the general population, however, is primarily associated with meat, dairy products, and fish (Beck et al. 1989a; Schaum et al. 1994; Schecter et al. 1994d, 1994e, 1996a). CDDs are transferred through the placenta to the fetus, by breast milk to infants and young children, and by lifelong dietary ingestion. Workers involved with incineration operations or those who have been or may be involved in the production, use, or disposal of trichlorophenol, phenoxyherbicides, hexachlorophene, pentachlorophenol and other compounds that contain impurities of CDDs are at a greater risk from exposure to CDDs and TEQs (Päpke et al. 1992; Schecter and Ryan 1988; Schecter et al. 1991). Individuals in the general population who may be exposed to potentially higher levels of CDDs include recreational and subsistence fishers (including many native Americans) and their families living in CDD-contaminated areas who consume large quantities of fish from contaminated waters (CRITFC 1994; Ebert et al. 1996), subsistence hunters such as the Inuit of Alaska who consume large quantities of wild game (particularly marine mammals) (Dewailly et al. 1993; Hebert et al. 1996; Norstrom et al. 1990), subsistence farmers and their families living in areas contaminated with CDDs who consume their own farm-raised beef and dairy products (EPA 1996b; McLachlan et al. 1994), individuals who live in the vicinity of an industrial or municipal incinerator, or individuals who live in the vicinity of the

126 hazardous waste sites where CDDs (and more especially where 2,3,7,8-substituted CDDs) have been detected (Gough 1991; Liem et al. 1991; Pohl et al. 1995; Riss et al. 1990; Wuthe et al. 1993).

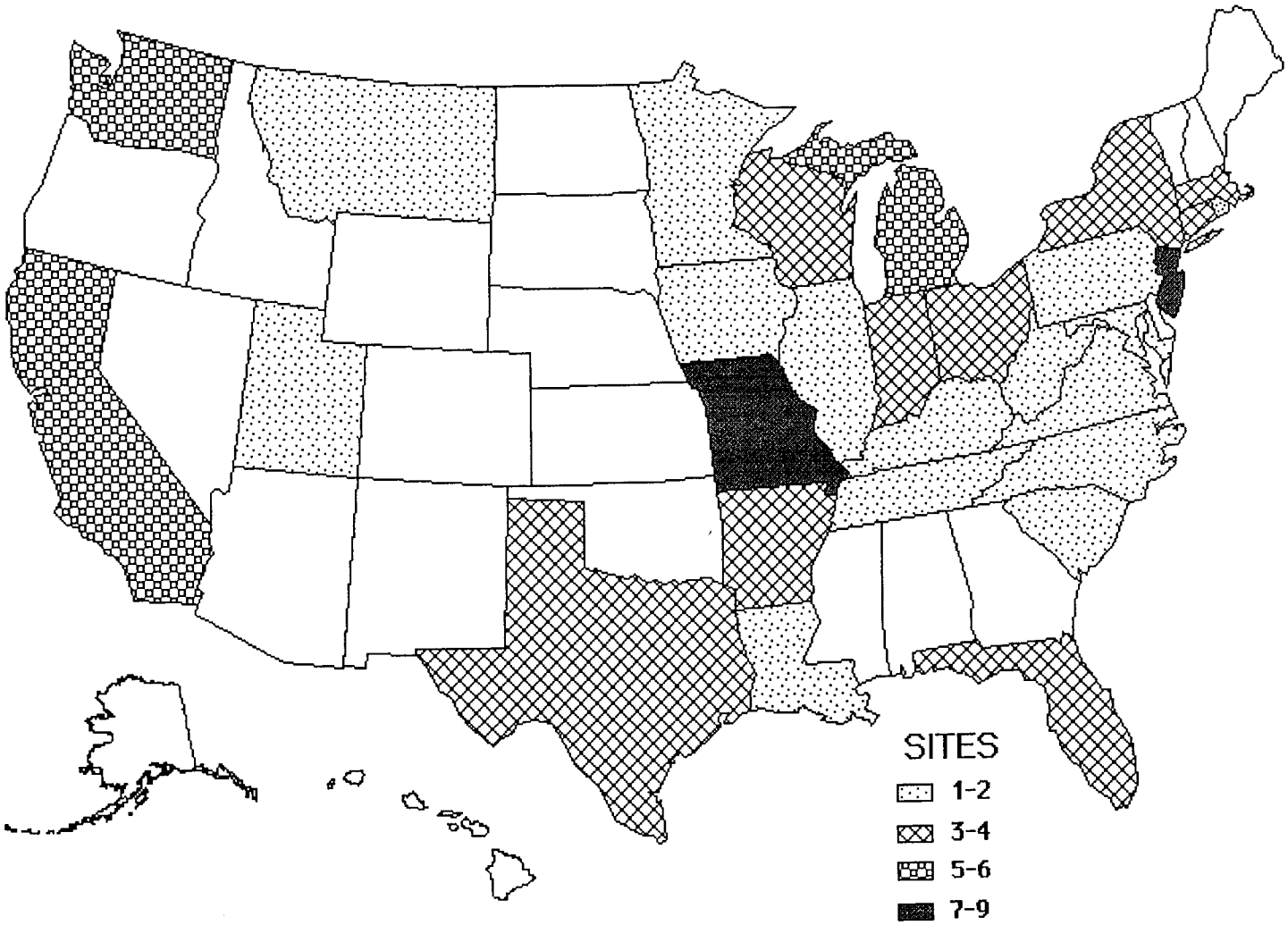
2,3,7,8-TCDD has been identified in at least 91 of 1,467 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1998). However, the number of sites evaluated for 2,3,7,8,-TCDD is not known. The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 90 are located in the United States and 1 is located in the Commonwealth of Puerto Rico (not shown). Total CDDs (including TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD) have been identified in 126, 105, 34, 43, 49, and 53 sites, respectively, of the 1,467 hazardous waste sites on the NPL. The frequency of these sites within the United States for total CDDS, TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD, respectively, can be seen in Figures 5-2 through 5-7. Of the 126 sites with total CDD detections, 125 are located in the United States and 1 site is located in the Commonwealth of Puerto Rico (not shown). Of the 105 sites with total TCDD detections, 104 are located in the United States and 1 site is located in the Commonwealth of Puerto Rico (not shown). Of the sites with PeCDD, HxCDD, HpCDD, and OCDD detections, all 34, 43, 49, and 53 sites, respectively, are located in the United States.

5.2 RELEASES TO THE ENVIRONMENT

CDDs have been measured in all environmental media including ambient air, surface water, groundwater, soil, and sediment. While the manufacture and use of chlorinated compounds, such as chlorophenols and chlorinated phenoxy herbicides, were important sources of CDDs to the environment in the past, the restricted manufacture of many of these compounds has substantially reduced their current contribution to environmental releases. It is now believed that incineration/combustion processes are the most important sources of CDDs to the environment (Zook and Rappe 1994). Important incineration/combustion sources include: medical waste, municipal solid waste, hazardous waste, and sewage sludge incineration; industrial coal, oil, and wood burning; secondary metal smelting, cement kilns, diesel fuel combustion, and residential oil and wood burning (Clement et al. 1985; Thoma 1988; Zook and Rappe 1994).

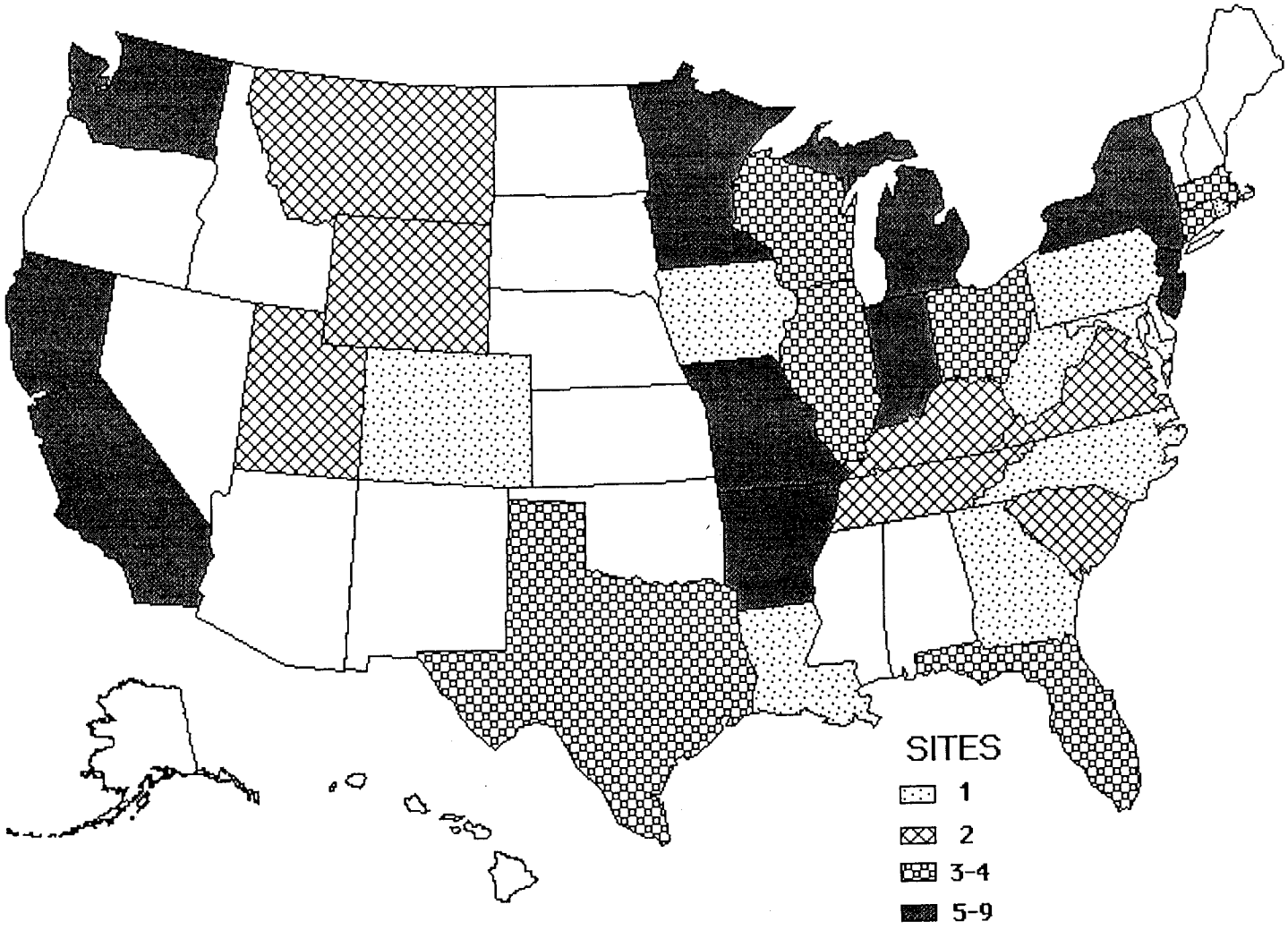
Emissions to the atmosphere from incineration and combustion sources result in the wide-spread distribution of CDDs. Consequently, CDDs are found at low levels in rural soils as well as in sediments of otherwise pristine waterbodies. Much of the CDD deposits from wet and dry deposition ultimately become components of urban runoff which enter rivers, streams, and estuaries directly or through stormwater outfalls and combined sewer overflows (CSOs). In a recent study, Huntley et al. (1997) used statistical

Figure 5-1. Frequency of NPL Sites with 2,3,7,8-TCDD Contamination



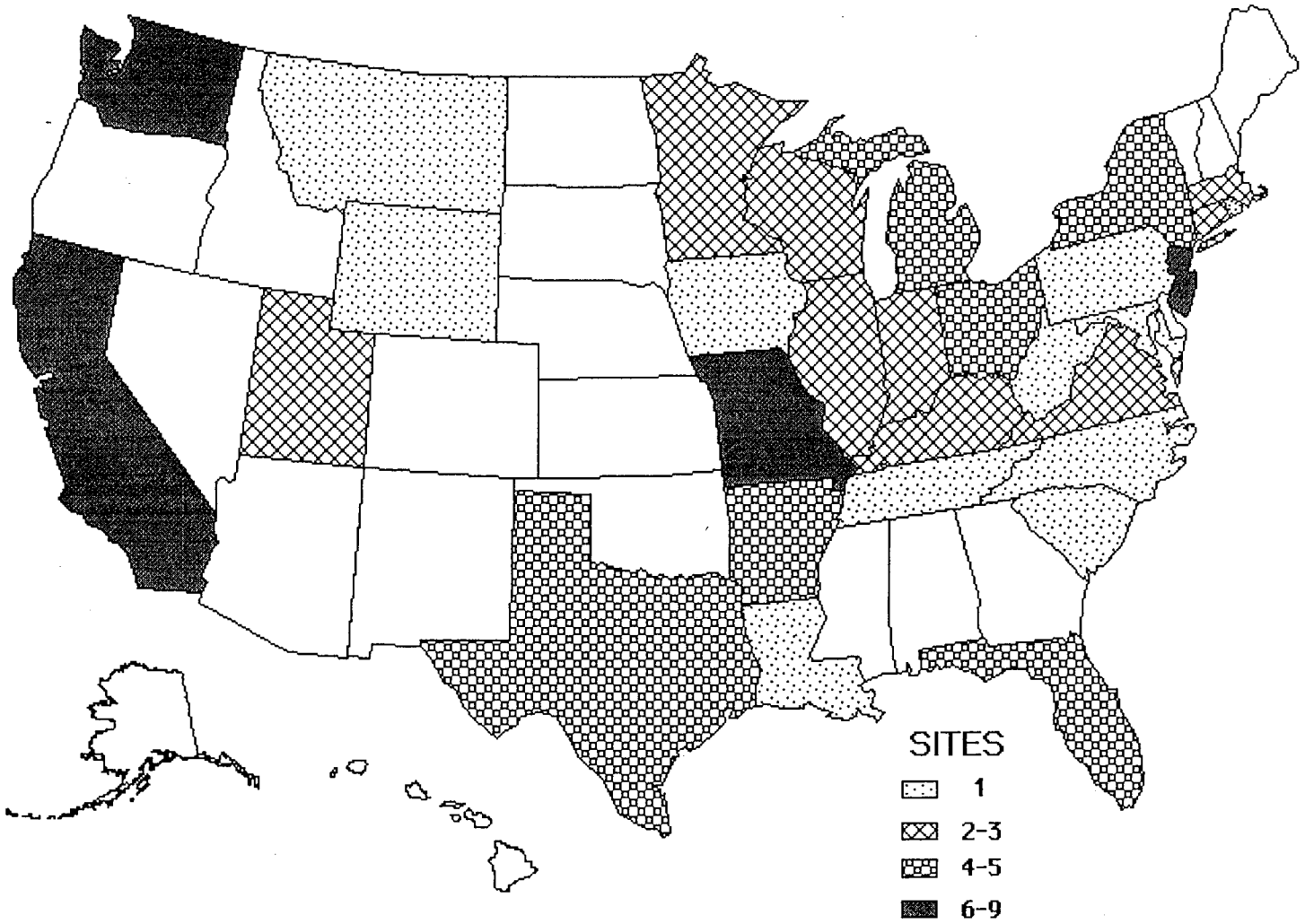
Derived from HazDat 1998

Figure 5-2. Frequency of NPL Sites with Total Dioxin Contamination



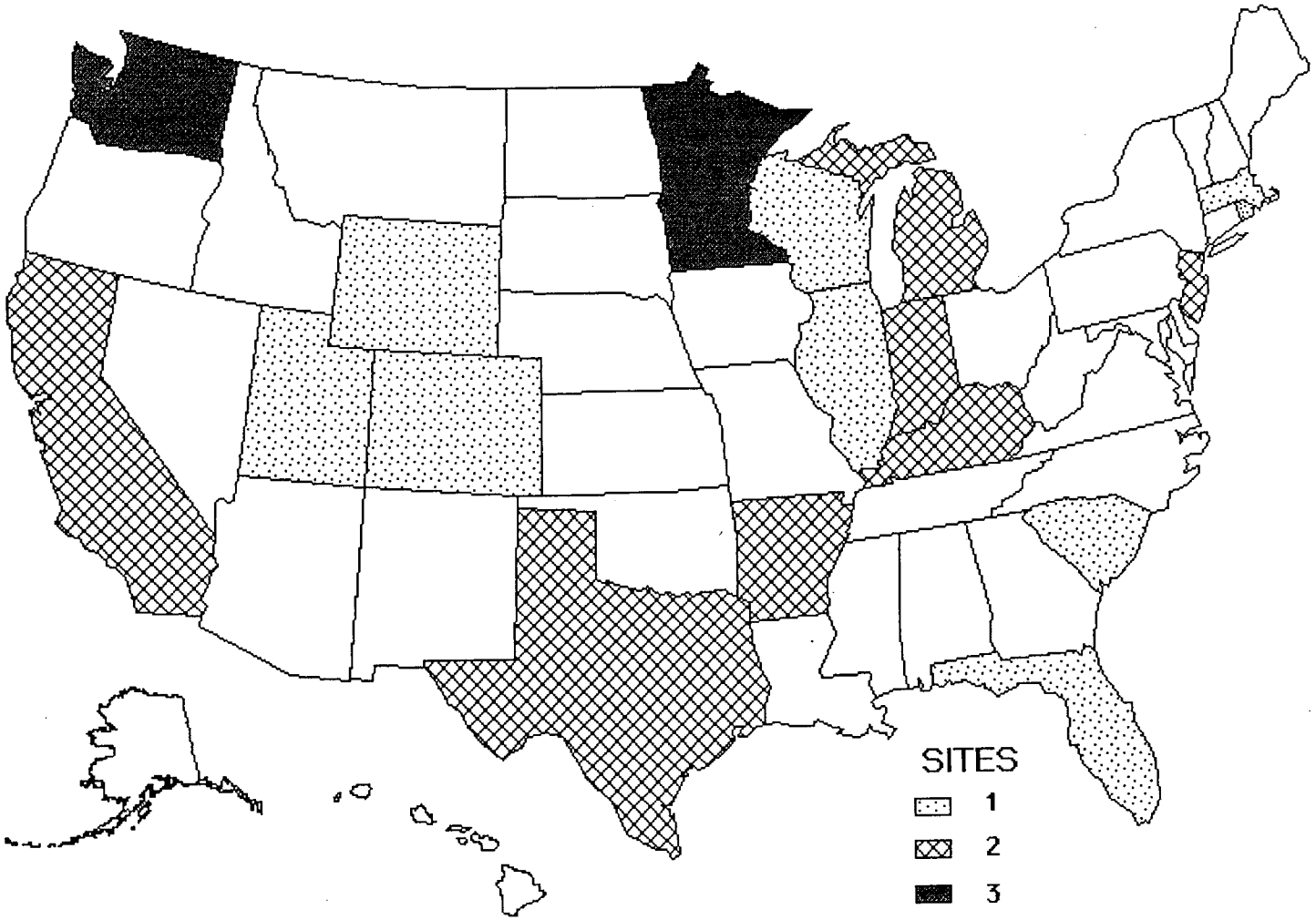
Derived from HazDat 1998

Figure 5-3. Frequency of NPL Sites with Tetra Dioxins Contamination



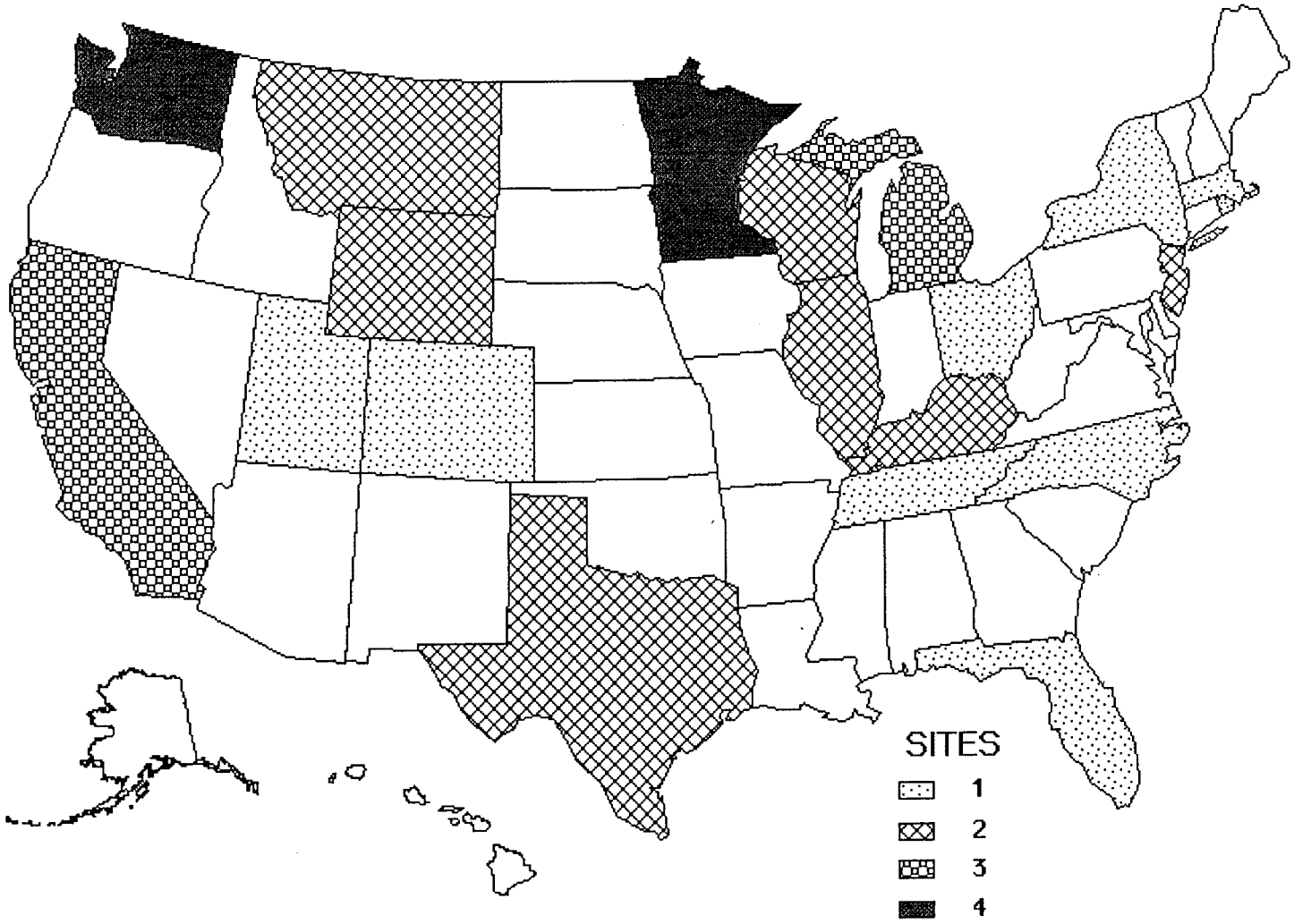
Derived from HazDat 1998

Figure 5-4. Frequency of NPL Sites with Penta Dioxins Contamination



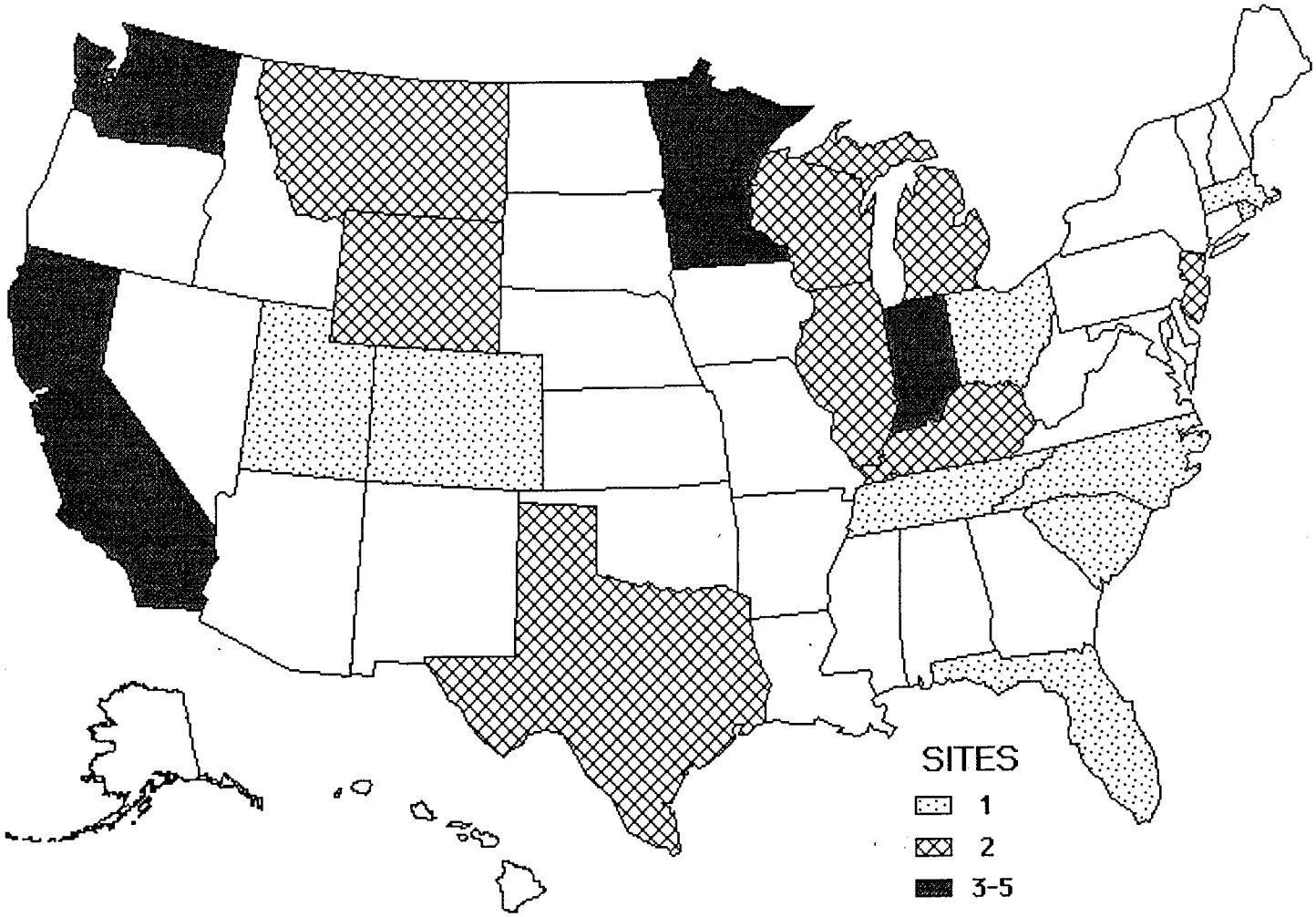
Derived from HazDat 1998

Figure 5-5. Frequency of NPL Sites with Hexa Dioxins Contamination



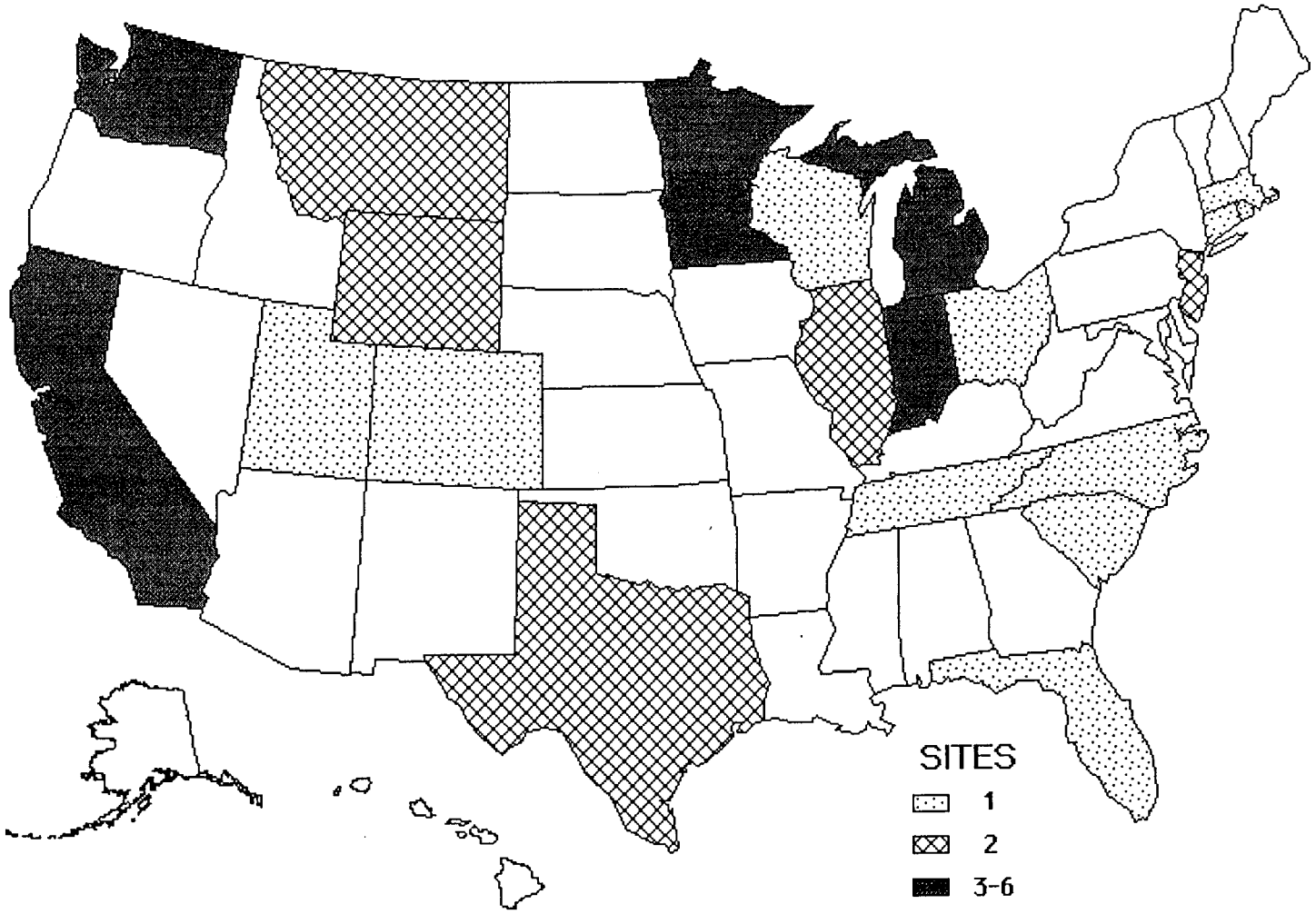
Derived from HazDat 1998

Figure 5-6. Frequency of NPL Sites with Hepta Dioxins Contamination



Derived from HazDat 1998

Figure 5-7. Frequency of NPL Sites with Octa Dioxins Contamination



Derived from HazDat 1998

pattern matching techniques (principal components analysis) to evaluate CDD congener patterns in sediment samples collected adjacent to several CSOs. According to these authors, the presence of these unique CDD/CDF congener patterns in sediment adjacent to CSOs suggested that these CSOs were a likely source given the industrial, residential, and stormwater inputs to the combined sewer overflow system. Such statistical techniques have been applied elsewhere to CDD congener pattern matching in an effort to identify specific sources of CDDs. Wenning et al. (1993a, 1993b) also applied principal components analysis to Newark Bay Estuary sediments and found that most of the congener fingerprint patterns were related to combustion/incineration sources. More recently, Ehrlich et al. (1994) applied polytopic vector analysis, a fingerprinting technique that "unmixes" the CDD/CDF patterns, and concluded that the primary sources of CDD/CDFs in Newark Bay Estuary sediments were combustion/incineration, sewage-related sources, and PCB-related sources. Statistical techniques that have proven useful for identifying sources of CDDs have recently been reviewed (Wenning and Erickson 1994). Future efforts to reduce the release of CDDs to the environment will require additional analysis of the distributional patterns of CDDs in environmental media, which may also provide information on sources still to be identified.

5.2.1 Air

The key sources of CDD releases to air are from anthropogenic combustion processes and the production and use of chemicals contaminated with CDDs. Some evidence suggests that natural combustion processes (e.g., forest fires or volcanic activity) may also be sources of CDDs, but to a much smaller extent. Toxics Release Inventory (TRI) data are not available for CDDs since CDD releases are not required to be reported (EPA 1995g).

Combustion Processes. Combustion processes generate CDDs, CDFs, and other halogenated aromatic compounds (Czuczwa and Hites 1984, 1986a, 1986b). Most of the direct releases of CDDs and CDFs from combustion processes are to the air (Czuczwa and Hites 1984, 1986a, 1986bc). CDDs and CDFs may be found in particulates released from the combustion of most types of organic material and limited evidence suggests that they may also result from trace chemical reactions in fire (Bumb et al. 1980; Crummett 1982; Safe 1990). The processes involved in the formation of CDDs and CDFs consist of numerous chemical reactions that occur during combustion of organic compounds in the presence of chlorinated material. The EPA has recently identified stationary source categories that release 2,3,7,8-TCDD TEQ to the atmosphere (EPA 1998j). The percentage contribution of the five highest source categories are: 68% from municipal waste incineration, 12.3% from medical waste incineration,

8.9% from Portland cement manufacture hazardous waste kilns, 3.5% from secondary aluminum smelting, and 3.0% from other biological incineration. These five source categories account for 95.9% of all stationary emissions of 2,3,7,8-TCDD TEQ to the air.

The "Trace Chemistries of Fire Hypothesis" suggests that CDDs and CDFs can also form during a variety of combustion processes including natural ones, such as forest fires and volcanic eruptions (Crummett 1982). However, there is very limited evidence suggesting that such natural processes could be minor sources of these compounds in the environment. Only data from one study were found that directly measured CDD/CDFs in actual emissions from forest fires. Tashiro et al. (1990) detected the concentration of total CDD/CDFs in air ranging from 15 to 400 pg/m^3. The samples were collected from fixed collectors 10 m above the ground and from aircraft flying through the smoke. Soil samples collected before the burn detected 43 ppt of OCDD in 1 of 4 samples tested. After the burn, OCDD was detected in 3 of 4 soil samples at concentrations of 46, 100, and 270 ppt. Because the small sample size precluded statistical analysis, no further conclusions were drawn by the authors. Thomas and Spiro (1995), however, estimated that forest and agricultural burning accounted for the third largest emission of CDD/CDF in the United States (30 kg/year), behind municipal waste incineration (200 kg/year) and hospital incinerators (40 kg/year) although the inclusion of agricultural burning, which may include acreage treated with long-lived organochlorine pesticides, may skew the values higher than would be expected from forest fires alone. Failure to find CDDs in ancient mummies or ancient frozen Eskimo tissues is another indication that the “Trace Chemistries of Fire Hypothesis” may have little bearing on human exposure (Ligon et al. 1989; Schecter et al. 1988; Tong et al. 1990). The EPA recently found elevated levels of 2,3,7,8-TCDD in two chickens that were traced to clay (used as an anti-caking additive in soybean animal meal) derived from clay deposits mined at the Kentucky-Tennesse Ball Clay Company in Crenshaw, Mississippi. (Chemical Regulation Reporter 1997a, 1997b). However, no information on the origin of the 2,3,7,8-TCDD, either natural or anthropogenic, was presented.

The issue of natural sources of CDD/CDF is interesting, but historical deposition records strongly implicate anthropogenic activity as the major source of CDD/CDFs (Thomas and Spiro 1996). These authors further suggest that the historic record on CDD/CDF deposition provided by sediment cores strongly implies that anthropogenic sources have been overwhelmingly dominant. Sediment cores from Siskwit Lake on a remote island in northern Lake Superior, provide a historic record of atmospheric CDD fluxes (Czuczwa and Hites 1986a). An 8-fold increase in the CDD/CDF deposition rate (from approximately 4–30 pg/cm^2/year) occurred between 1940 and 1970, corresponding to a great expansion in the

industrial use of chlorine (Thomas and Spiro 1996). The decrease in deposition rate of about 30% (from 30 to 24 pg/cm^2/year) from 1970 to the mid 1980s parallels decreased production and use of chlorophenols (pesticide registrations for 2,4,5-T and Silvex were discontinued in 1983 and 1984, respectively) (IARC 1977; Sine 1990) and reductions in municipal incinerator emission resulting from improvements in design, pollution controls, and operation of these facilities (Thomas and Spiro 1996). It is difficult to reconcile these trends with predominantly natural sources, especially since the total area of U.S. forests consumed by forest fires diminished by more than a factor of 4 between 1940 and 1970 through more effective fire control (Thomas and Spiro 1996).

Although the production of CDDs during combustion processes are highlighted here, most samples from combustion sources show a complex mixture of isomers and congeners of CDDs and CDFs which vary in their relative concentrations (Kolenda et al. 1994; Nestrick and Lamparski 1983; Vikelsoe et al. 1994). CDDs have been detected in emissions (flue gas and fly ash) from municipal, hazardous waste, and industrial incinerators (Buser 1987; Oppelt 1991; Sedman and Esparza 1991; Schecter 1983). Combustion of materials, such as vegetation treated with phenoxy acetic acid herbicides, paper and wood treated with chlorophenols, pesticide-treated wastes, and polyvinylchloride (PVC) in the presence of naturally occurring phenols, may lead to CDDs and CDD precursors (Arthur and Frea 1989). PVC is known to yield a small amount of chlorobenzene upon pyrolysis, which in turn thermally decomposes to CDDs and CDFs (Lustenhouwer et al. 1980). CDDs have also been detected in fly ash from an oil-fired power plant, in city dust, in commercial sludge fertilizer, in particulate deposits in car and truck mufflers, in exhaust from vehicles powered with leaded and unleaded gasoline and diesel fuel, in cigarette smoke, and in soot from home fireplaces and from PCB and chlorinated benzene contaminated transformer fires (Bumb et al. 1980; Hutzinger et al. 1985; Lofroth and Zebuhr 1992; Marklund et al. 1987, 1990; Muto and Takizawa 1989; Schecter 1983; Thoma 1988). Dichloroethane, the chlorinated additive in leaded gasoline, is also a source of CDDs (Marklund et al. 1987). The dichloroethane acts as a scavenger to prevent the deposition of lead compounds in engines (Safe 1990). Although the data indicate that CDDs result from diverse processes, the relative contributions of these sources and other unidentified sources to the presence of CDDs in the atmosphere are not known.

A mixture of CDDs (TCDD, PeCDD, HxCDD, HpCDD, OCDD) has been found in emissions (both particles and flue gases) from various combustion sources, including municipal incinerators, power plants, wood burning, home heating systems, and petroleum refining (Chiu et al. 1983; Czuczwa and Hites 1984; Gizzi et al. 1982; Nessel et al. 1991; Thoma 1988; Thompson et al. 1990). In individual samples of

emissions from an urban incinerator, HxCDDs and OCDD were often the most abundant CDDs found, although the homologue pattern can be quite variable (Gizzi et al. 1982). Emission of TCDD from municipal waste combustion ranged from 0.018 ng/m^3 to 62.5 ng/m^3 depending on the type of combustion facility (Roffman and Roffman 1991). A municipal solid waste incinerator sampled in 1988 contained an average TCDD concentration of 0.0012 ng/m^3, where OCDD was present at 1.2 ng/m^3, and HxCDD was present at >1 ng/m^3 (Nessel et al. 1991). In another study, no TCDDs were found in emissions from hazardous waste or municipal waste incinerators; the levels of PeCDD found in the emissions from municipal waste incinerators were three orders of magnitude higher than from hazardous waste incinerators (Oppelt 1991). Fly ash from a municipal incinerator and from coal-fired power plants was analyzed to study the CDD congener distributions typical of combustion samples (Czuczwa and Hites 1984). OCDD was the most abundant CDD in all fly ash samples. Coal fly ash samples differed significantly from municipal incinerator fly ash samples. Although some CDDs were detected in coal fly ash, no TCDDs or PeCDDs were detected. CDDs were present in much lower concentrations in fly ash from coal-fired power plants than in fly ash from a municipal incinerator. The levels of OCDD in the coal fly ash samples (2.2 ppb and 3.8 ppb) were at least 100 times lower than those found in the municipal incinerator fly ash (400 ppb). No isomers of TCDD were detected in municipal incinerator fly ash samples with a detection limit of 100 ppt (Czuczwa and Hites 1984).

CDDs have been detected in chimney soot samples from various home heating systems using unleaded heating oil, coal, and wood in Germany (Thoma 1988). A Canadian study of wood-burning stoves detected only OCDD in particulates from the stack emissions (Wang et al. 1983). Open-air burning of PCP-treated wood produced levels of CDDs ranging from 2 ppb (TCDD) to 187 ppb (OCDD) (Chiu et al. 1983). Combustion of untreated wood also produces CDDs (TCDD, PeCDD, HxCDD, HpCDD, OCDD) (Clement et al. 1985). Samples of bottom ash and chimney ash from 2 wood-burning stoves, 1 open fireplace, and outdoor open-air burning had detectable levels of CDDs ranging from 0.3 to 33 ppb. For each homologous class, the total concentrations ranged from not detectable to 11 ppb. Detection limits were equal to 10 ppt for TCDD and PeCDD and 50 ppt for HxCDD, HpCDD, and OCDD. The open-air burning ash produced the highest total CDD concentration of 33 ppb, with HpCDD (11 ppb) and OCDD (10 ppb) being the most abundant (Clement et al. 1985).

Fires involving capacitors or transformers containing chlorobenzene and PCBs are also sources of CDDs and CDFs. For example, in the transformer fire in the New York State Office Building in Binghamton, NY, TCDD, PeCDD, HxCDD, HpCDD, and OCDD were found in soot samples at levels ranging from

<2 ppm (PeCDD) to 7 ppm (HpCDD) (Tiernan et al. 1985). CDFs were more abundant and were detected at higher concentrations ranging from 28 to 1,920 ppm in soot.

Recently, Wikstrom et al. (1996) studied formation of CDDs, CDFs, and chlorobenzenes in the combustion process. These authors monitored combustion of an artificial fuel where the chlorine level and source were varied in the artificial waste. Different levels of organic chlorine (PVC) and inorganic chlorine ($CaCl_2$⁄6$H_2$0) were added to the fuel. When the level of chlorine in the fuel was <1%, there was no correlation between the quantities of CDDs, CDFs, and chlorobenzenes present. However, when the chlorine level was >1%, increased formation rates were noted for CDDs, CDFs, and chlorobenzenes.

Production and Use of Contaminated Chemicals and Certain Herbicides. CDDs are known trace contaminants of certain chlorinated industrial chemicals like chlorophenols (Buser 1987). CDDs can inadvertently form as by-products during the manufacture of chlorophenols. Since the 1930s, PCP and the tri- and tetrachlorophenols have gained recognition as fungicides, herbicides, insecticides, and precursors in the synthesis of other pesticides.

PCP was developed primarily for use as a wood preservative but has also been used as an herbicide on pineapple and sugarcane plantations. It has also been employed as a molluscicide against schistosomiasis, a severe human parasitic disease prevalent in much of tropical Asia, Africa, and South America (Hutzinger et al. 1985). The major contaminant of commercial PCP is OCDD, which may be present at concentrations between 500 and 1,500 mg/kg (ppm) (Dobbs and Grant 1979; Miller et al. 1989a). PCP may also contain mixed isomers of HxCDD and HpCDD (Pereira et al. 1985). It is currently registered as a restricted-use pesticide for use as a wood preservative (Sine 1990).

2,3,7,8-TCDD forms during the manufacture of 2,4,5-TCP. 2,4,5-TCP has been used in cooling towers and in paper, pulp, and leather processing (Hutzinger et al. 1985). 2,4,5-TCP was used to produce the bactericide hexachlorophene and phenoxy-herbicides like 2,4,5-trichlorophenoxy acids (2,4,5-T). 2,4,5-T, in turn, was used in the production of a wide variety of herbicides including Silvex (2-[2,4,5-trichloro-phenoxy]propionic acid) and Agent Orange (Hutzinger et al. 1985). Hexachlorophene, which is currently under EPA suspension, is reported to contain <15 µg/kg (ppb) 2,3,7,8-TCDD (IARC 1977; Sine 1990). 2,3,7,8-TCDD is an unwanted by-product formed during the production of hexachlorophene (Freeman et al. 1986). The 2,3,7,8-TCDD produced is primarily contained in still-bottom waste (waste oils) remaining after hexachlorophene is purified (Freeman et al. 1986). Still-bottom waste and other oils were used in the

early 1970s for dust control on roads, parking lots, horse arenas, and other sites around Missouri (Freeman et al. 1986). The herbicide 2,4,5-T produced commercially prior to 1965 contained up to 30 mg/kg (ppm) or more 2,3,7,8-TCDD (IARC 1977). The level of 2,3,7,8-TCDD in commercial 2,4,5-T was reduced to <0.05 mg/kg (ppm), and most of the commercial 2,4,5-T available before its registration was discontinued in the United States in 1983 contained <0.02 mg/kg (ppm) 2,3,7,8-TCDD (IARC 1977; Sine 1990). Chlorophenoxy herbicides, such as 2,4-D, are typically formulated as esters or amine salt derivatives (IARC 1986b). Of 16 samples of 2,4-D formulations from Canada analyzed for CDDs in the early 1980s, 8 of 9 ester formulations and 4 of 7 amine salt formulations were contaminated (IARC 1986b). The 2,4-D ester formulations contained 0.2–1.8 mg/kg (ppm) 1,3,6,8-TCDD (the only TCDD isomer detected), while the 2,4-D amine salt formulations contained 0.02–0.3 mg/kg (ppm) 1,3,6,8-TCDD (IARC 1986b). It should be noted that 1,3,6,8-TCDD is not one of the toxic CDDs with respect to mammals; however, 2,3,7,8-substituted CDDs/CDFs have been reported in 2,4-D from Russia (Schecter et al. 1993).

Agricultural and wartime uses of trichlorophenol-based herbicides such as 2,4,5-T and Silvex also have resulted in release of 2,3,7,8-TCDD at low concentrations in many countries (EPA 1987k). 2,4,5-T was used in aerial spraying operations for weed control on crops, along fence rows, ditch banks, farm roadways, pastures, and rangeland (Bovey 1980). Non-farm uses of 2,4,5-T included tree and bush control on rights-of-way, roadways, fire lanes, and railroads (Bovey 1980). Agent Orange, used as a defoliant in the Vietnam War from 1962 to 1970, was contaminated with an average of 2 ppm of 2,3,7,8-TCDD (Czuczwa and Hites 1986a, 1986b; Wolfe et al. 1985). An estimated 10–11 million gallons were applied in South Vietnam (EPA 1987k; Wolfe et al. 1985). This volume of Agent Orange contained an estimated 368 pounds of 2,3,7,8-TCDD (Wolfe et al. 1985). Agent Orange is an equal parts mixture of the butyl esters of 2,4,5,-T and 2,4-dichlorophenoxyacetic acid (2,4-D) (Josephson 1983). These herbicides were used extensively in silviculture for control of deciduous trees in conifer forests before their use was discontinued (EPA 1987k). The use of Silvex, a herbicide closely related to 2,4,5-T, was discontinued in the United States in 1984 (Sine 1990).

Industrial accidents have also released high levels of CDDs into the air. In 1976, at least 1.3 kg (2.87 pounds) of 2,3,7,8-TCDD was released into the air as a result of an industrial accident at the ICMESA chemical plant near Seveso, Italy, that was involved in 2,4,5-TCP synthesis (Cerlisi et al. 1989; Mocarelli et al. 1991). The 2,3,7,8-TCDD release contaminated a populated area of about 2.8 km^2 (1.08 mi^2) (Mocarelli et al. 1991).

2,3,7,8-TCDD has been detected in air samples collected at 9 of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). Total CDDs have been detected in air samples collected at 10 of the 126 NPL sites where they have been detected in some environmental media. Total TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD have been detected in air samples at 10, 3, 3, 3, and 1 sites of the 105, 34, 43, 49, and 53 sites, respectively, where they have been detected in some environmental media (see Table 5-1).

5.2.2 Water

CDDs can enter water by a number of different mechanisms including urban runoff, combined sewer overflows (CSOs), and direct discharge by industrial facilities and publicly-owned treatment works (POTWs); deposition of particulates from combustion sources, runoff and drift from the use of chlorophenol-based pesticides; and leaching from chlorophenol-containing waste sites (Huntley et al. 1997; Muir et al. 1986a; Periera et al. 1985; Shear et al. 1996). Direct application or drift of 2,4,5-T or Silvex into water has also resulted in release of TCDD to surface water (Norris 1981); however, the contribution of CDDs from pesticide drift is now negligible since most CDD-containing pesticides have been banned. The migration of chemical wastes containing CDDs from disposal sites has resulted in contamination of surface water and groundwater (HazDat 1998).

CDDs/CDFs, specifically 2,3,7,8-TCDD and 2,3,7,8-TCDF, are also present in effluent and sludges from pulp and paper mills that employ the bleached kraft process (Clement et al. 1989; EPA 1991b; Swanson et al. 1988). 2,3,7,8-TCDD was detected in 7 of 9 bleached pulps at concentrations ranging from not detected (<1 ppt) to 51 ppt (median 4.9 ppt; mean 13 ppt) (Amendola et al. 1989). It was also detected in waste waters from 4 of 5 paper mills at levels ranging from not detected (<0.006 ppt) to 3.6 ppt (Amendola et al. 1989).

During 1988, the EPA and the U.S. pulp and paper industry jointly conducted a survey of 104 pulp and paper mills in the United States to measure concentrations of CDDs in effluent, sludge, and paper (EPA 1990d). This study is commonly called the 104-Mill Study and includes all U.S. mills where wood pulps are bleached with chlorine or chlorine derivatives. Higher chlorinated CDDs/CDFs are typically found in effluent when chlorine dioxide is used, but not when elemental chlorine is used. In 1992, the pulp and paper industry conducted its own survey (NCASI 1993). As part of an effort to develop revised effluent guidelines and standards for the pulp and paper industry, the EPA recently published the development

Table 5-1. Number of NPL Sites Where CDDs Have Been Detected in One or More Environmental Media[a]

Medium	2,3,7,8-TCDD[b]	**Total CDDs[c]**	Total TCDDs[d]	Total PeCDDs[e]	Total HxCDDs[f]	Total HpCDDs[g]	Total OCDDs[g]
Air	9	**10**	10	3	3	3	1
Surface water	9	**14**	10	1	4	4	6
Groundwater	15	**32**	21	3	10	14	16
Soil[i]	61	**94**	71	21	29	34	38
Sediment	17	**31**	22	7	10	9	13
Fish	11	**13**	12	1	0	0	1
Game animals	1	**1**	1	0	0	0	0
Total sites where chemical was detected	91	**126**	105	34	43	49	53

[a] A total of 1,467 hazardous waste sites have been identified on the NPL nationwide
[b] Includes only 2,3,7,8-TCDD (CAS# 001746-01-6)
[c] Includes all dioxins identified in footnotes d, e, f, g, and h.
[d] Includes 2,3,7,8-TCDD and other tetra Cdds (CAS# 41903-57-5)
[e] Includes PeCDDs (CAS# 039227-61-7 and 040321-76-4)
[f] Includes HxCDDs (CAS# 019408-74-3, 034465-46-8, 057653-85-7)
[f] Includes HpCDDs (CAS# 035822-46-9 and 037871-00-4)
[h] Includes OCDD (CAS# 003268-87)
[i] Soil contamination sites include those defined as:
1. surface/top soil
2. subsurface soil, or
3. soil depth not specified.

CDD = chlorinated dibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; NPL = National Priorities List; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: HazDat 1998

document for the guidelines and standards being proposed for this industry (EPA 1993a). This development document presents estimates of annual discharges of two congeners, 2,3,7,8-TCDD and 2,3,7,8-TCDF in effluents (from wastewater treatment systems) from this industry as of January 1993.

The joint EPA/paper industry study of 104 pulp and paper mills provides an estimate of the release of 2,3,7,8-TCDD and 2,3,7,8-TCDF in bleached pulp, waste water sludge, and waste water effluent from the U.S. pulp and paper industry as of mid-to-late 1988 (EPA 1990d). This was a time in the industry's history when only limited use of pulping and bleaching technologies and operating practices that demonstrated potential to reduce the formation of TCDDs and TCDFs had been implemented. In this study 2,3,7,8-TCDD was detected at 90 and 56% of the kraft and sulfite mills, respectively, that were surveyed, and no mill was found to be free of 2,3,7,8-TCDD/TCDF. For bleached pulp, the mean 2,3,7,8-TCDD concentration was 7.5 ppt (maximum 56 ppt) for kraft hardwoods, 12 ppt (maximum 116 ppt) for kraft softwoods, 7.1 ppt (maximum 15 ppt) for sulfite hardwoods, and 3.5 ppt (maximum 3.5 ppt) for sulfite softwoods. Mean waste water effluent concentrations of 2,3,7,8-TCDD were 0.076 ppt for kraft mills (maximum 0.64 ppt) and 0.013 ppt (maximum 0.023 ppt) for sulfite mills. Waste water sludges contained mean 2,3,7,8-TCDD concentrations of 101 ppt for kraft mills (maximum 1,390 ppt) and 13 ppt (maximum 58 ppt) for sulfite mills. Furthermore, for all kraft mills, about 38% of the 2,3,7,8-TCDD was partitioned to pulps, 33% to waste water sludges, and 29% to waste water effluents.

The NCASI (1993) report found that <10% of pulp and paper mills had 2,3,7,8-TCDD and 2,3,7,8-TCDF concentrations in effluent above the detection limits of 10 ppq and 100 ppq, respectively; however, none of the more highly congener groups were measured. Similar results were obtained in the short- and long-term sampling reported for 18 mills (EPA 1993a). 2,3,7,8-TCDD and 2,3,7,8-TCDF were detected at four and nine mills, respectively. Waste water sludges at 75–90% of all mills contained <10 ppt of 2,3,7,8-TCDD and <100 ppt of 2,3,7,8-TCDF (NCASI 1993). Similar results were reported in the EPA (1993a) report except that 2,3,7,8-TCDD and 2,3,7,8-TCDF were found in sludges in 64 and 85%, respectively, of the mills sampled. NCASI (1993) reported that almost 90% of bleached pulps contained <2 ppt of 2,3,7,8-TCDD and <20 ppt of 2,3,7,8-TCDF. For bleached pulps, the mean 2,3,7,8-TCDD concentration was 0.9 ppt (maximum 10 ppt) and the mean 2,3,7,8-TCDF concentration was 6 ppt (maximum 323 ppt). The mean waste water effluent concentration of 2,3,7,8-TCDD was 0.006 ppt (maximum 0.08 ppt) and 0.031 ppt (maximum 0.510 ppt) for 2,3,7,8-TCDF. Waste water sludges contained a mean 2,3,7,8-TCDD concentration of 11 ppt (maximum 133 ppt) and 11 ppt (maximum 735 ppt) for 2,3,7,8-TCDF. In this study, mean pulp, waste water effluents, and waste water sludge concentrations of 2,3,7,8-TCDD all

declined by a factor of about 10 from those cited in the 104 Mill Study (EPA 1990d). Overall, NCASI (1993) reports a 90% reduction in TEQs generated by pulp and paper mills from 1988 to 1992 for all 2,3,7,8-TCDDs and 2,3,7,8-TCDFs.

2,3,7,8-TCDD has been detected in surface water and groundwater samples collected at 9 and 15 sites of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). Total CDDs have been detected in surface and groundwater samples collected at 14 and 32 of the 126 NPL sites where they have been detected in some environmental media. Total TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD have been detected in surface water samples collected at 10, 1, 4, 4, and 6 sites and in groundwater samples collected at 21, 3, 10, 14, and 16 of the 105, 34, 43, 49, and 53 NPL sites, respectively, where these homologues have been detected in some environmental media (see Table 5-1).

5.2.3 Soil

Historically, CDDs have been deposited onto soil through pesticide applications and disposal of CDD-contaminated industrial wastes, and via land application of paper mill sludges (EPA 1991b). Currently, however, atmospheric fall-out of CDD-laden particulates and gases appears to be the predominant source of CDDs to soil (Hutzinger et al. 1985).

The commercial production of trichlorophenol, as well as various derivative products such as 2,4,5-T and other biocides, has yielded large quantities of waste products containing substantial concentrations of CDDs. Extensive contamination of the environment with 2,3,7,8-TCDD occurred in Missouri in the early 1970s as a result of the spraying of horse arenas, roads, and parking lots with mixtures of used oil and chemical waste (Tiernan et al. 1985). The chemical waste, formed during the manufacture of 2,4,5-TCP and then used to make hexachlorophene, contained several hundred ppm of 2,3,7,8-TCDD (Tiernan et al. 1985). Several thousand gallons of this waste were dispersed over a sizable area of southwestern and eastern Missouri during the 1970s. Concentrations of 2,3,7,8-TCDD in soil samples from selected contaminated sites throughout Missouri ranged from 30 to 1,750 ppb (Tiernan et al. 1985). Concentrations of 2,3,7,8-TCDD in soil samples from Times Beach, Missouri, which had been heavily contaminated, ranged from 4.4 to 317 ppb (Tiernan et al. 1985).

In Seveso, Italy, an explosion occurred during the production of 2,4,5-T and a cloud of toxic material including 2,3,7,8-TCDD was released (Cerlisi et al. 1989; MMWR 1988; Mocarelli et al. 1991). Debris

from the cloud covered an area of approximately 700 acres (2.8 km^2). The total amount of 2,3,7,8-TCDD released during the accident was estimated to be 1.3 kg. Soil samples from this industrial accident were measured in three areas: Zone A, the most contaminated zone where residents were evacuated; Zone B, the moderately contaminated area where residents were advised not to eat locally raised produce; and Zone R, where 2,3,7,8-TCDD contamination in soil was lowest of the three areas. Mean soil concentrations in these 3 areas were: 230 $\mu g/m^2$ (maximum 5,477 $\mu g/m^2$) in Zone A, 3 $\mu g/m^2$ (maximum 43.9 $\mu g/m^2$) in Zone B, and 0.9 $\mu g/m^2$ (maximum 9.7 $\mu g/m^2$) in Zone R (MMWR 1988).

The migration of chemical waste containing CDDs from disposal sites has also resulted in environmental contamination of sediment. For example, at Love Canal in Niagara Falls, New York, where an estimated 200 tons of 2,4,5-TCP production waste were disposed of during the 1940s and early 1950s, 2,3,7,8-TCDD was detected at high concentrations (up to several hundred ppb) in storm sewer sediments (Smith et al. 1983; Tiernan et al. 1985).

2,3,7,8-TCDD has been detected in soil and sediment samples collected at 61 and 17 sites of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). Total CDDs have been detected in soil and sediment samples collected at 94 and 31 of the 126 NPL sites where they have been detected in some environmental media. Total TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD have been detected in soil samples at 71, 21, 29, 34, and 38 sites and in sediment samples at 22, 7, 10, 9, and 13 sites of the 105, 34, 43, 49, and 53 NPL sites, respectively, where these homologues have been detected in some environmental media (see Table 5-1).

5.3 ENVIRONMENTAL FATE

Combustion generated CDDs may be transported long distances (as vapors or associated with particulates) in the atmosphere (Czuczwa and Hites 1986a, 1986b; Tysklind et al. 1993). They may eventually be deposited on soils, surface waters, or plant vegetation as a result of dry or wet deposition. CDDs (primarily MCDD, DCDD, TrCDD) will slowly volatilize from the water column, while the more highly chlorinated CDDs will adsorb to suspended particulate material in the water column and be transported to the sediment (Fletcher and McKay 1993; Muir et al. 1992). CDDs deposited on soils will strongly adsorb to organic matter. CDDs are unlikely to leach to underlying groundwater but may enter the atmosphere on soil dust particles or enter surface waters on soil particles in surface runoff. Low water solubilities and high lipophilicity indicate that CDDs will bioconcentrate in aquatic organisms, although as a result of their

binding to suspended organic matter the actual uptake by such organisms may be less than predicted. This is also true of uptake and bioconcentration by plants, although foliar deposition and adherence may be significant.

5.3.1 Transport and Partitioning

Combustion processes appear to have contributed to the ubiquity of CDDs in the environment (Hites and Harless 1991; Tysklind et al. 1993). CDDs have relatively long residence times in the atmosphere, and combustion-generated CDDs associated with particulates can become distributed over large areas (Tysklind et al. 1993). During transport in the atmosphere, CDDs are partitioned between the vapor phase and particle-bound phase (Hites and Harless 1991). However, because of the very low vapor pressure of CDDs, the amount present in the vapor phase generally is negligible as compared to the amount adsorbed to particulates (Paustenbach et al. 1991). The two environmental factors controlling the phase in which the congener is found are the vapor pressure and the atmospheric temperature (Hites and Harless 1991). Congeners with vapor pressure $<10^{-8}$ mm Hg will be primarily associated with particulate matter while congeners with a vapor pressure $>10^{-4}$ mm Hg will exist primarily in the vapor phase. Those chemicals with vapor pressures between these values can be found in both the vapor phase and associated with particulates (Eisenreich et al. 1981). With a reported vapor pressure ranging from $7.4x10^{-10}$ to $3.4x10^{-5}$ mm Hg, 2,3,7,8-TCDD falls into the intermediate category.

The detection of CDDs in sediments from Siskiwit Lake, Isle Royale, suggests that CDDs can be transported great distances in air (Czuczwa and Hites 1986a, 1986b). Because this lake is landlocked on a wilderness island in Lake Superior, the only way that CDDs could reach these sediments is by atmospheric fall-out (i.e., by wet and dry deposition). Similar amounts of CDDs were also found in Lake Huron and Lake Michigan sediments, which indicates that atmospheric transport is a source of CDDs found on these Great Lake sites (Czuczwa and Hites 1986a, 1986b; Hutzinger et al. 1985). Atmospheric deposition of TCDD to Lake Erie may contribute up to 2% of the annual input of TCDD to the lake (Kelly et al. 1991). Through pattern analysis of herring gull monitoring data, Hebert et al. (1994) provided evidence that the sources of CDDs in Great Lakes food chains were mainly atmospheric, with the exception of 2,3,7,8-TCDD in Lake Ontario, and several CDDs in Saginaw Bay in Lake Huron where point sources were implicated.

CDDs are physically removed from the atmosphere via wet deposition (scavenging by precipitation), particle dry deposition (gravitational settling of particles), and gas-phase dry deposition (sorption of CDDs in the vapor phase onto plant surfaces) (Rippen and Wesp 1993; Welschpausch et al. 1995). Precipitation (rain, sleet, snow) is very effective in removing particle-bound CDDs from the atmosphere (Hites and Harless 1991; Koester and Hites 1992). Table 5-2 summarizes the average ppt scavenging ratios and percentage of washout due to particulates for congener groups of both CDDs and CDFs collected at two sites in Indiana. The scavenging ratio is the ratio of the concentration of the congener group in rain to the atmospheric concentration of the congener group and is a measure of the effectiveness of rain in removing the congener groups from the atmosphere. Table 5-2 also summarizes the percentages of the congener groups scavenged as particles in rain rather than as dissolved solutes in rain. Total rain scavenging ratios ranged from 10,000 to 150,000; HpCDDs and OCDD (the congeners most strongly associated with particulates) were the congeners scavenged most efficiently (Hites and Harless 1991; Koester and Hites 1992).

Environmental fate modeling of CDDs requires knowledge of a number of fundamental physical and chemical parameters, such as water solubility, vapor pressure, Henry's law constant, octanol-water partition coefficient (K_{ow}), and organic carbon partition coefficient (K_{oc}). CDDs are a class of high molecular weight, highly hydrophobic compounds. Although the class contains 8 homologues (congener groups) and 75 congeners, solubility values are available for only a handful of these congeners (Doucette and Andren 1988). CDDs have very low water solubilities, with solubility decreasing with increasing chlorine substitutions (Doucette and Andren 1988). The water solubility of 2,3,7,8-TCDD ranges from $7.9x10^{-6}$ to $33.2x10^{-4}$ mg/L (Shiu et al. 1988). See Table 3-2 for the water solubilities for specific congeners. Water solubilities at 25 EC for the congener groups have been estimated as follows: MCDD, 0.278–0.417 mg/L; DCDD, $3.75x10^{-3}$–$1.67x10^{-2}$ mg/L; TrCDD, $4.75x10^{-3}$–$8.41x10^{-3}$; TCDD, $7.9x10^{-6}$ to $6.3x10^{-4}$ mg/L; PeCDD, $1.18x10^{-4}$ mg/L; HxCDD, $4.42x10^{-6}$ mg/L; HpCDD, $2.4x10^{-6}$–$1.9x10^{-3}$ mg/L; and OCDD, $0.1x10^{-9}$–$7.4x10^{-8}$ mg/L (ASTER 1995; Doucette and Andren 1988; HSDB 1997; McCrady and Maggard 1993; Shiu et al. 1988).

CDDs generally exhibit very low vapor pressures, with the tendency of decreasing vapor pressure with increasing chlorine substitution (Friesen et al. 1985; Rordorf 1986, 1989). At 25 EC, the vapor pressure of 2,3,7,8-TCDD ranges from $7.4x10^{-10}$ to $3.4x10^{-5}$ mm Hg (HSDB 1997; Rordorf 1989). See Table 3-2 for the vapor pressures of specific congener groups. Vapor pressures at 25 EC for the other congener groups have been estimated as follows: MCDD, $9.0x10^{-5}$–$1.3x10^{-4}$ mm Hg; DCDD, $9.0x10^{-7}$–$2.9x10^{-6}$ mm Hg;

Table 5-2. Rain Scavenging Ratios (RS) and Percent Washout Due to Particulates (%W) for CDDs and CDFs in Ambient Air in Two Midwest Cities

Congener Group	Bloomington, IN		Indianapolis, IN	
	RS	%W	RS	%W
TCDD[a]	–	–	–	–
PeCDD	10,000	50	30,000	67
HxCDD	10,000	88	26,000	69
HpCDD	62,000	93	91,000	78
OCDD	90,000	80	150,000	60
TCDF	22,000	21	33,000	24
PeCDF	14,000	54	18,000	35
HxCDF	11,000	77	15,000	74
HpCDF	34,000	88	32,000	79
OCDF	21,000	52	41,000	87
Total CDD/CDF	—	68	—	64

[a]Rarely detected; no calculations performed

Sources: Hites and Harless 1991; Koester and Hites 1992

HpCDD = heptachlorodibenzo-*p*-dioxin; HpCDF = heptachlorodibenzofuran; HxCDD = hexachlorodibenzo-*p*-dioxin; HxCDF = hexachlorodibenzofuran; OCDD = octachlorodibenzo-*p*-dioxin; OCDF = octachlorodibenzofuran; PeCDD = pentachlorodibenzo-*p*-dioxin; PeCDF = pentachlorodibenzofuran; TCDD = tetrachlorodibenzo-*p*-dioxin; TCDF = tetrachlorodibenzofuran

$6.46x10^{-8}$–$7.5x10^{-7}$; TCDD, $7.4x10^{-10}$–$4.0x10^{-3}$ mm Hg; PeCDD, $6.6x10^{-10}$ mm Hg; HxCDD, $3.8x10^{-11}$ mm Hg; HpCDD, $5.6x10^{-12}$–$7.4x10^{-8}$ mm Hg; and OCDD, $8.25x10^{-13}$–$1.68x10^{-12}$ mm Hg (HSDB 1997; McCrady and Maggard 1993; Rordorf 1989; Shiu et al. 1988). CDDs can be found in both the vapor and particle-bound phases (Eitzer and Hites 1989a; Hites and Harless 1991), with the low vapor pressure of OCDD resulting in its enrichment in the particulate phase in the atmosphere. When this particulate matter is deposited on water, OCDD-enriched sediments will result (Eitzer 1993). The less chlorinated CDD congeners (TCDD and PeCDD) occur in greater proportion in the vapor and dissolved phases of air and rain, whereas the more chlorinated congeners (HpCDD and OCDD) are associated with the particulate-bound phases (EPA 1991d). Data from one study of CDDs in the ambient atmosphere of Bloomington, IN, found that vapor-to-particle ratios for individual CDDs ranged from 0.01 to 30 and were dependent on the ambient temperature and the compound's vapor pressure (Eitzer and Hites 1989b). Since the less-chlorinated CDDs have higher vapor pressures, they are found to a greater extent in the vapor phase (Eitzer and Hites 1989a). As air moves, photodegradation of the vapor-phase CDDs occurs and they are lost more readily than the particulate-bound CDDs. Vapor-phase CDDs are not likely to be removed from the atmosphere by wet or dry deposition (Atkinson 1991), although this is a primary removal process for particulate-bound CDDs. Wet or dry deposition could result in greater concentrations of the more chlorinated CDDs reaching soil or water surfaces and eventually sediment (EPA 1991d). All CDDs are found to some extent in both the vapor phase and bound to particulates. At warmer temperatures (28 EC), CDDs, particularly the MCDDs, DCDDs, TrCDDs, and TCDDs will have a greater tendency to exist in the vapor phase. At cooler temperatures (16–20 EC and <3 EC), all CDDs will have less propensity to exist in the vapor phase and greater propensity to adsorb to particulates (Shroy et al. 1985). At a constant temperature, there is a positive relationship between increasing numbers of chlorine atoms on the molecule and decreased propensity to exist in the vapor phase relative to particulate adsorption (Eitzer and Hites 1989b; Paustenbach et al. 1991; Shroy et al. 1985).

CDDs are removed from the water column to a minor extent by volatilization to the atmosphere, with binding to particulates and sediment, or bioaccumulation by aquatic biota being more significant processes (Fletcher and McKay 1993; Muir et al. 1992; Paustenbach et al. 1992). CDDs have Henry's law constants ranging from 1.31×10^{-6} to 146×10^{-6} atm-m^3/mol (Shiu et al. 1988). These values indicate that volatilization from water is likely to be a slow, with the transfer rate controlled by the gas-phase resistance (i.e., the rate is controlled by slow diffusion through the air) (Lyman et al. 1982; Shiu et al. 1988). The more chlorinated homologous classes (TCDD, PeCDD, HxCDD, HpCDD, OCDD) have lower Henry's law constant values than the less chlorinated homologous classes (MCDD, DCDD, TrCDD). Thus,

volatilization from the water column is not expected to be a very significant loss process for the TCDD through OCDD congeners as compared to adsorption to particulates. In general, the Henry's law constants decrease with increasing chlorine number as a result of the decrease in vapor pressure and water solubility (Shiu et al. 1988). Volatilization half-lives for 2,3,7,8-TCDD were calculated for ponds and lakes (32 days) and for rivers (16 days) (Podoll et al. 1986). The primary removal mechanism for CDDs from the water column is sedimentation, with 70–80% of the CDDs being associated with the particulate phase (Muir et al. 1992). The remainder was associated with dissolved organic substances. CDDs bound to sediment particles may be resuspended in the water column if the sediments are disturbed. This could increase both the transport and availability of the CDDs for uptake by aquatic biota (Fletcher and McKay 1993).

Generally, CDDs are characterized by low vapor pressure, low aqueous solubility, and high hydrophobicity, suggesting that these compounds strongly adsorb to soil and that their vertical mobility in the terrestrial environment is low (Eduljee 1987b). In general, higher chlorinated CDDs also volatilize more slowly from soil and water surfaces than do lower chlorinated ones (Hutzinger et al. 1985). Nash and Beall (1980) reported that only 12% of 2,3,7,8-TCDD applied to bluegrass turf as a component of emulsifiable Silvex volatilized over a 9-month period. Because CDDs (particularly the more highly chlorinated PCDD, HxCDD, HpCDD, and OCDD) strongly adhere to soil and exhibit low solubility in water, leaching of CDDs would be unlikely if water were the only transporting medium. Instead, wind and erosion can cause the mixing and transport of CDD-contaminated soil. As a result of erosion, surface soil contaminated with CDDs is either blown away by wind or washed via surface water runoff into rivers, lakes, and streams, with burial in the sediments being the predominant fate of CDDs sorbed to soil (Hutzinger et al. 1985).

Adsorption is an important process affecting transport of hydrophobic compounds such as CDDs. The organic carbon fraction of the soil is believed to be the most important factor governing the degree of adsorption of hydrophobic organic contaminants. CDDs adsorb more strongly to soils with a higher organic carbon content than to soils with low organic carbon content (Yousefi and Walters 1987). Because of their very low water solubilities and vapor pressures, CDDs found below the surface soil (top few mm) are strongly adsorbed and show little vertical migration, particularly in soil with high organic carbon content (Yanders et al. 1989). Vertical movement of CDDs in soil may result from the saturation of sorption sites of the soil matrix, migration of organic solvents, or human or animal activity (Hutzinger et al. 1985). Adsorption/desorption of 2,3,7,8-TCDD in contaminated soils was studied by Des Rosiers (1986). Soil samples were taken from an abandoned 2,4,5-T manufacturing facility and a scrap metal yard in New

Jersey and from horse arenas, roadways, and residential property in Missouri. Historically, these samples were contaminated with either chemical residues or waste oils containing 2,3,7,8-TCDD. Mean log organic carbon partition coefficient (K_{oc}) values ranged from 7.39 to 7.58 (Des Rosiers 1986). This K_{oc} range indicates that 2,3,7,8-TCDD is immobile in soil (Swann et al. 1983). However, the mobility of 2,3,7,8-TCDD in soil will increase if organic co-solvents that can solubilize 2,3,7,8-TCDD are present in the soil (Podoll et al. 1986). This situation might occur at a hazardous waste site. In one study, only 1.5% of the CDDs applied to soil surfaces had leached to a depth of 2.5 cm below the soil surface after 15 months. Leaching of the CDDs through the soil was primarily associated with carriers such as petroleum oil (Orazio et al. 1992).

Most CDDs entering surface waters are associated with particulate matter (dry deposition of atmospheric particles) and eroded soil particulates contaminated with CDDs (Hallett and Brooksbank 1986). In the aquatic environment, significant partitioning of CDDs from the water column to sediment and suspended particulate organic matter may occur. Dissolved CDDs will partition to suspended solids and dissolved organic matter (detritus, humic substances) and are likely to remain sorbed once in the aquatic environment. From suspended sediment and water data collected from the Niagara River on the New York-Canada border, it was found that CDDs were strongly associated with suspended sediment (Hallett and Brooksbank 1986). Concentrations of total TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD in raw water ranged from below detection limits to 3.6 pg/L (3.6 ppq), while the concentration of these same homologue groups in suspended sediments ranged from below detected limits to 228 pg/g (ppt) (Hallett and Brooksbank 1986). The more highly chlorinated congeners (HxCDD, HpCDD, and OCDD) predominated in both water and suspended sediment samples.

A model has been developed to describe the vertical transport of low-volatility organic chemicals in soil (Freeman and Schroy 1986). The model was used to make predictions on the transport of 2,3,7,8-TCDD at the Eglin Air Force Base Agent Orange biodegradation test plots (Freeman and Schroy 1986). Trenches 10 cm deep were dug in the soil, and Agent Orange containing 40 ppb of 2,3,7,8-TCDD was applied to the trench bottom. The model predicted a vertical movement of 2,3,7,8-TCDD, buried in 1972, through the soil column. Soil-column-profile data confirm the vertical movement of 2,3,7,8-TCDD from core samples taken in 1984 (Freeman and Schroy 1986). The 2,3,7,8-TCDD in the Eglin Air Force Base biodegradation plots moved through the entire 10 cm of the soil column in 12 years (Freeman and Schroy 1986). The rates of migration and loss of 2,3,7,8-TCDD in contaminated soil were studied under natural conditions in experimental plots at the Dioxin Research Facility, Times Beach, Missouri (Yanders et al. 1989). The

TCDD concentration profiles of sample cores taken at Times Beach in 1988 (mean range 78–160 ppb) were virtually the same as those in cores taken in 1984 (mean range 76–162 ppb). The results show that little movement and essentially no loss due to volatilization of 2,3,7,8-TCDD had occurred in the experimental plots in the four years since the Dioxin Research Facility was established (Yanders et al. 1989).

CDDs are characterized by low water solubilities and high lipophilicities. K_{ow} values range from 10^4 to 10^{12} for MCDD through OCDD, with K_{ow} values increasing relative to increasing chlorination (Table 3-2). Because of these physicochemical properties, CDDs are expected to adsorb to bedded and suspended sediments and to bioaccumulate in aquatic organisms.

The bioconcentration factor (BCF) is the ratio of the concentration of CDDs in an organism over the concentration of CDDs in water. The BCF values for CDDs can be estimated from their K_{ow} values, and a number of regression equations are available for this purpose (Bysshe 1990). Experimentally measured BCFs for selected CDD congeners in various aquatic species are summarized in Table 5-3. Measurements of the bioconcentration of CDDs tend to increase with the degree of chlorination up to TCDDs, and then decrease as chlorination continues to increase up to the OCDD congener (Loonen et al. 1993). The more highly chlorinated congeners, such as OCDD, appear to have the lowest bioconcentration potential either because they are less bioavailable because of their rapid adsorption to sediment particles (Servos et al. 1989a, 1989b) or because their large molecule size may interfere with transport across biological membranes (Bruggeman et al. 1984; Muir et al. 1986a, 1986b).

The hydrophobic nature of CDDs, combined with their great affinity for organic carbon, suggests that a major proportion of CDDs in the aquatic environment is sorbed to organic matter and sediment. Because only a minute fraction of CDDs are dissolved in the natural environment, bioconcentration is not the primary route of exposure for most aquatic organisms. Whereas the term bioconcentration is defined as the uptake of a chemical from water only, the term bioaccumulation refers to the combined uptake of a chemical from both dietary sources (e.g., food) and water. A bioaccumulation factor (BAF) that includes the ingestion route of uptake can be calculated based on fish uptake from water, food, and sediment (Sherman et al. 1992).

The primary route of exposure to CDD congeners for lower trophic organisms (e.g., phytoplankton and various aquatic invertebrates) is uptake from the water column or from interstitial water (between sediment

Table 5-3. Bioconcentration Factors (BCFs) for Aquatic Organisms

Organism	Congener	Exposure period (days)	Media	BCF	References
Aquatic plants					
Oedogonium cardiacum *Elodea nuttali* *Ceratophylum demeusum*	2,3,7,8-TCDD	1–50	Water/sediment	208–2,083	Isensee 1978; Tsushimoto et al. 1982; Yockim et al. 1978
Invertebrates					
Physa sp. *Helosoma* sp. *Daphnia magna*	2,3,7,8-TCDD	1–32	Water/sediment	702–7,125	Isensee 1978; Yockim et al. 1978
Chironomus sp. *Hexagenia* sp. *Paragnetina* sp. *Pteronarcys* sp. *Acroneuria* sp.	1,3,6,8-TCDD	4	Water/sediment	1,375–18,439 (sand) 304–111,345 (silt)	Muir et al. 1983
Chironomus sp. *Hexagenia* sp. *Paragnetina* sp. *Pteronarcys* sp.	OCDD	4	Water/sediment	173–2,854 (sand) 331–2,296 (silt)	Muir et al. 1983
Fish					
Carp (*Cyprinus carpio*)	2,3,7,8-TCDD	71	Water	66,000	Cook et al. 1991
Rainbow trout fry (*Oncorhynchus mykiss*)	1,2,3,7-TCDD 1,3,6,8-TCDD 1,2,3,4,7-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,4,6,7-HpCDD OCDD	5	Water	874–1,577 1,400–2,938 810 1,715–2,840 1,059–1,790 34–136	Muir et al. 1986a, 1986b

Table 5-3. Bioconcentration Factors (BCFs) for Aquatic Organisms (continued)

Organism	Congener	Exposure period (days)	Media	BCF	References
Fathead minnow (*Pimephales promelas*)	1,2,3,7-TCDD 1,3,6,8-TCDD 1,2,3,4,7-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,4,6,7-HpCDD OCDD	5	Water	2,018–2,458 5,565–5,840 1,200–1,647 2,630–5,834 513–515 2,226	Muir et al. 1986a, 1986b
Fathead minnow (*Pimephales promelas*)	2,3,7,8-TCDD	71	Water	128,000	Cook et al. 1991
Fathead minnow (*Pimephales promelas*)	2,3,7,8-TCDD 2,3,7,8-TCDD		Water/sediment Water/sediment	2,500 5,800	Tsushimoto et al. 1982 Adams et al. 1986
Mosquitofish (*Gambusia affinis*)	OCDD	104	Experimental lake	>9,000	Servos et al. 1989b
White sucker (*Catostomus commersoni*)	2,3,7,8-TCDD		Water/sediment	4,875	Yockim et al. 1978

BCF = bioconcentration factor; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

particles). Certain benthic organisms accumulate highly lipophilic compounds (e.g., PCBs and CDDs/CDFs) from water at the water/sediment interface (the concentration of a lipophilic compound is generally higher at this interface than in the water column) and via intake of phytoplankton, zooplankton, and suspended particulate materials that contain higher concentrations of these chemicals than the surrounding water (Porte and Albaiges 1993; Pruell et al. 1993; Secor et al. 1993). For the higher trophic level organisms, such as foraging fish, predaceous fish, and piscivorous wildlife, the predominant route of exposure is via food chain transfer, with negligible contributions from CDDs in water and sediment (Muir and Yarechewski 1988). Exposure through direct consumption of CDD-contaminated sediment and detritus may occur in some bottom-feeding species such as carp and white suckers (Kuehl et al. 1987a, 1987b; Servos et al. 1989a, 1989b). Under natural conditions, in which a high proportion of these hydrophobic CDD compounds are sorbed to suspended and dissolved organic matter, direct uptake of these CDDs from water is not expected to be substantial (Muir et al. 1986a, 1986b). The estimated BCFs in such cases may not be a good indicator of the experimental bioaccumulation measured in the field. Another reason for the difference between estimated BCFs and experimentally measured bioaccumulation values is the ability of some aquatic organisms to metabolize and eliminate specific CDD congeners from their bodies and thereby change the congener profile pattern in their tissues.

Preferential bioconcentration and bioaccumulation of 2,3,7,8-TCDD and other 2,3,7,8-substituted CDDs by aquatic organisms have been reported (Branson et al. 1985; Kuehl et al. 1985, 1987a, 1987b, 1987c; Opperhuizen 1986; Paustenbach et al. 1992). In water-only exposure studies, BCF values for fish exposed to 2,3,7,8-TCDD ranged from 37,900 to 128,000 (Cook et al. 1991; Mehrle et al. 1988). Much lower BCF values ranging from 1,400 to 5,840 and 34 to 2,226 have been reported for fish exposed to 1,3,6,8,-TCDD and OCDD, respectively (Muir et al. 1986a, 1986b). These BCF values are approximately two orders of magnitude less than would be predicted using the K_{ow} values. Similarly, the lower BCFs for HpCDD in fathead minnows and OCDD in rainbow trout fry relative to the other CDDs tested resulted from lower uptake efficiencies from water. Elimination half-lives for TCDDs and PeCDDs were similar and rapid, averaging about 2.6 days in trout fry and 3 days in minnows. Elimination half-lives for HxCDD and HpCDD were longer, averaging about 16 days in rainbow trout and 20 days in fathead minnows (Muir et al. 1986b). The results of these studies also indicate that BCFs of the higher chlorinated CDDs (HxCDD, HpCDD, OCDD) from water are much lower than would be predicted based on their K_{ow} values. Servos et al. (1989a, 1989b) also noted that the BCF values were less than predicted based on the K_{ow} values, and these authors suggest that BCFs reported in the literature may underestimate the true BCF, unless the BCFs were calculated using truly dissolved CDD concentrations in the water column rather than

total dissolved concentrations, which would include complexes with large molecules of dissolved organic carbon.

BCF values measured in fish exposed to both water and sediment were much lower than equivalent exposures to water only and ranged from 2,500 to 5,800 (Adams et al. 1986; Cook et al. 1991; Tsushimoto et al. 1982) (Table 5-3). Loonen et al. (1993) also reported that bioaccumulation of CDDs was reduced in the presence of sediment and that the effects of sediment increased with increasing hydrophobicity (degree of chlorination) of the congeners. BCFs were reduced by 15–82% for various CDD/CDF congeners, with the greatest reduction associated with OCDD.

The bioavailability of CDDs/CDFs from municipal incinerator fly ash and sediment to freshwater fish has been studied in experimental situations. Like the BCF and BAF values, the biota-sediment-accumulation factor (BASF) (ratio of contaminant concentration in the organism normalized to lipid content to the concentration in fly ash or sediment, normalized to organic carbon content) generally decreased with an increasing degree of chlorination (Kuehl et al. 1985, 1987b, 1987c). The BASF values for benthic (bottom-dwelling) fish (e.g., carp, catfish) are generally higher than for those pelagic (water column) species (e.g., bass, trout, sunfish) because of the higher lipid content and increased exposure to contaminated sediments for the benthic species (Paustenbach et al. 1992).

Several authors have studied the disposition and metabolism of CDDs in fish. Studies on the disposition of 2,3,7,8-TCDD in rainbow trout and yellow perch indicate that fatty tissues (visceral fat, carcass, skin, and pyloric caeca) typically contain the bulk of 2,3,7,8-TCDD (78–90%) with only a small percentage (2–5%) associated with the skeletal muscle (Kleeman et al. 1986a, 1986b). For other congeners, such as 1,3,6,8-TCDD and OCDD, the greatest proportion of the total body burden is concentrated in the bile, with lesser concentrations in liver > caeca > kidney > spleen > skin > muscle (Muir et al. 1986a, 1986b). Differences in the distribution among various species may be a function of the exposure pathway (i.e., dietary versus water uptake) and differences in metabolic breakdown rates. For example, both the parent compound and metabolites of 2,3,7,8-TCDD and 1,3,6,8-TCDD were present in the bile of fish exposed under laboratory conditions (Branson et al. 1985; Muir et al. 1986a, 1986b). Kleeman et al. (1986b) reported the presence of several polar metabolites in the gall bladder of yellow perch exposed to a single dose of ^{14}C- 2,3,7,8-TCDD. One week later, the gall bladder, skin, skeletal muscle, and kidneys were removed. In contrast to liver, muscle, and kidney where the parent compound accounted for 96–99% of the extractable ^{14}C, the gall bladder contained almost entirely 2,3,7,8-TCDD metabolites, at least one of which

was a glucuronide conjugate. Although the metabolic breakdown was slow, it is clear that CDDs can be transformed by fish to polar metabolites that are subsequently excreted in the bile.

Freshwater aquatic invertebrates have been shown to bioaccumulate CDDs/CDFs through water, sediment, and food pathways (Isensee 1978; Muir et al. 1983; Yockim et al. 1978). The range in experimentally determined BCF values for freshwater invertebrates is presented in Table 5-3. As discussed previously, exposure to CDDs from sediment and water containing dissolved organic material markedly decreases the BCF values, especially for the more highly chlorinated CDDs. Sediment-dwelling organisms (e.g., *Chironomous sp.* larvae and *Hexagenia sp.* nymphs), stoneflies, and other predaceous nymphs showed poor accumulation of OCDD in comparison to 1,3,6,8-TCDD (Muir et al. 1983). The lower bioaccumulation of OCDD was attributed to greater adsorption of the OCDD onto sediment particles and organic matter, and the reduced uptake across biological membranes due to large molecular size. The potential ingestion of sediments during burrowing activities by sediment-dwelling insects was believed to result in greater tissue concentrations of CDDs than those observed for predaceous insects. It is also possible that predaceous insects may metabolize 1,3,6,8-TCDD more effectively, leading to a greater rate of elimination. Sediment-dwelling organisms are important food sources for fish and other predaceous insects; consequently, if rapid elimination of 1,3,6,8-TCDD and low accumulation of OCDD occur in the natural environment, bioaccumulation of these congeners in trophically higher-level organisms may not be significant (Muir et al. 1983).

Marine invertebrates have also shown an ability to bioaccumulate CDDs/CDFs to varying degrees in their tissues (Brown et al. 1994; Cai et al. 1994; Conacher et al. 1993; Hauge et al. 1994; Rappe et al. 1991), although no information on BCF values was found in the literature. Interestingly, several investigators have reported that shellfish species (crustaceans and molluscs) are better indicators of CDD/CDF contaminant levels than fish because their tissues contain larger numbers and higher residues of CDD/CDF congeners in addition to the 2,3,7,8-TCDD congeners and other 2,3,7,8-substituted congeners that are selectively accumulated in fish species (Brown et al. 1994; Conacher et al. 1993; Rappe et al. 1991). This is in contrast to what is observed in fish and fish-eating birds, in which there is selective retention of congeners with the 2,3,7,8-substitution positions occupied, which may be due to an increased ability to metabolize and eliminate non-2,3,7,8-substituted CDD/CDF congeners (Brown et al. 1994; Rappe et al. 1991). The use of shellfish species as target organisms in CDD/CDF-monitoring studies is recommended as these species provide a better overall representation of both the magnitude and congener-specific nature of the environmental contamination (Petreas et al. 1992). Conacher et al. (1993) present an example where

use of a shellfish species provides a much higher estimate of exposure to CDDs/CDFs as well as to total CDD equivalent toxicity (TEQs) than use of a fish species. This difference in congener bioaccumulation profiles between fish and shellfish species is a result of the ability of fish to metabolize CDDs/CDFs. Both the parent congeners and metabolites of 2,3,7,8-TCDD and 1,3,6,8-TCDD were present in the bile of fish exposed under laboratory conditions (Branson et al. 1985; Muir et al. 1986a). Kleeman et al. (1986a, 1986b) reported the presence of several polar metabolites, including glucuronide conjugates, in various fish exposed to 2,3,7,8-TCDD. Despite the slowness of the metabolic breakdown processes, it is clear that CDDs can be transformed within fish to polar metabolites that are subsequently excreted with the bile. It does not appear from the results obtained in studies conducted to date that shellfish species have the same ability to metabolize and eliminate non-2,3,7,8-substituted CDDs/CDFs (Brown et al. 1994; Cai et al. 1994).

It is apparent from the available data regarding the substantial bioaccumulation potential of CDDs/CDFs in aquatic organisms (particularly the 2,3,7,8-substituted congeners) as well as data on the extent of contamination of fish and shellfish in various freshwater and marine waterways, that ingestion of contaminated fish and shellfish is an important exposure pathway for CDDs/CDFs in humans.

CDDs have been found to accumulate in both surface and rooted aquatic vegetation, with BCF values ranging from 208 to 2,083 (Table 5-3) (Isensee 1978; Tsushimoto et al. 1982; Yockim et al. 1978). Corbet et al. (1983) reported that a rooted plant species (*Potemageton pectimatus*) and a surface-dwelling duckweed (*Lemna* sp.) accumulated concentrations of 1,3,6,8-TCDD of 280 and 105 ng/g (dry weight), respectively, following exposure to water containing 1,000 ng/L (ppt). The maximum concentrations were observed 8 days post-application and represented 6% of the total TCDD applied. These results are similar to those reported by Tsushimoto et al. (1982) in an outdoor pond study, in which a maximum bioaccumulation of 2,3,7,8-TCDD in the pond weeds *Elodea nuttali* and *Ceratophyllon demersum* equivalent to a BCF of 130 occurred after 5 days of exposure. In both studies, the tissue concentrations reached equilibrium in approximately 20 days and remained constant until the end of the experiment (approximately 58 and 170 days, respectively). These experimental data indicate that CDDs can accumulation in aquatic plant species through waterborne exposure.

Like many fish, several species of fish-eating birds have shown the ability for preferential bioaccumulation of 2,3,7,8-TCDD and other 2,3,7,8-substituted CDDs and TCDFs. Jones et al. (1994) monitored TEQ values for 2,3,7,8-TCDD in double-crested cormorants from three of the Great Lakes: Superior, Michigan,

and Huron. Biomagnification factors (BMF, the ratio of the concentration of TCDD-equivalents in bird eggs to concentrations in forage fish) were found to range from 11.7 to 56.8 (mean, 31.3). In another study, all of the CDDs and CDFs detected in double-crested cormorant and Caspian tern eggs were 2,3,7,8-substituted (Yamashita et al. 1992). Concentrations of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HXCDD, 1,2,3,6,7,8-HXCDD, 1,2,3,7,8,9-HXCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD ranged from 5.3 to 20, 3.2 to 9.4, 10 to 20, 3.6 to 11, and 7.8 to 16 pg TEQ/g, respectively, for double-crested cormorant eggs, and 8.2 to 22, 3.3 to 6.4, 8.7 to 17, 2.4 to 6.0, and 9.7 to 21 pg TEQ/g, respectively, for Caspian tern eggs. This same pattern was also reported to occur in California peregrine falcons and their eggs (Jarman et al. 1993). For this species, mean concentrations of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD and OCDD in eggs were 5.7, 11, 2, 11, 1.3, 3.8, and 5.3, respectively. Fish-eating birds are exposed to CDDs primarily through their diet. A rapid decline in contaminant levels in eggs of fish-eating birds, therefore, reflects a rapid decrease in contaminant levels of their prey. This has been shown to occur in Great blue heron chicks in British Columbia (Sanderson et al. 1994) in areas where CDD/CDF levels in pulp and paper mill effluents decreased substantially within a few years. The Great blue heron chicks also showed an increased hepatic microsomal ethoxyresorufin O-deethylase (EROD) activity in the areas of highest contamination. This indicates that the induction of cytochrome P-450 1A1 has occurred, and that the Ah-receptor-mediated process, by which 2,3,7,8-TCDD and related chemicals exert their toxicities, has been activated.

Ankley et al. (1993) studied the uptake of persistent polychlorinated hydrocarbons by four avian species at upper trophic levels of two aquatic food chains. Concentration of 2,3,7,8-TCDD toxic equivalents (TEQs) were evaluated in Forster's tern and common tern chicks and in tree-swallow and red-winged-blackbird nestlings from several areas in the watershed. Young birds accumulated small concentrations of 2,3,7,8-TCDD and several other 2,3,7,8-substituted CDDs and CDFs, including 1,2,3,6,7,8-HxCDD, 2,3,7,8-TCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,7,8-PeCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD. The general trend in concentrations of CDDs from the greatest to least was Forster's tern - common tern > tree swallow > red-winged blackbird. The similarity in concentrations between the two tern species is expected given that they are both piscivores and their similar life histories and the close proximity of the two colonies. The greater concentrations in the tree swallows than in the red-winged blackbirds were somewhat unexpected given the presumed similarity of the diets (both species are insectivores). The authors suspect that the red-winged blackbirds foraged more on relatively uncontaminated upland food sources than the tree swallows, which fed primarily on chironomids emerging from the bay.

2,3,7,8-TCDD is generally considered to be bioavailable to terrestrial birds primarily through ingestion of TCDD-laden food items and soil particles (Nosek et al. 1992). These authors, using H^3TCDD-administered suspensions in various environmental matrices, found that 30% of the dose absorbed from suspensions of earthworms, 33% absorbed from soil suspensions, 41% absorbed from suspensions of paper mill sludge solids, and 58% absorbed from a suspension of crickets. These authors also reported that the percentage of the cumulative TCDD dose translocated to an individual egg was 1.1% for the first 15 eggs laid and that the percentage was not affected by the order in which the eggs were laid. Assuming an adult female could lay 30 eggs, 35% of the hen TCDD body burden could be translocated to all eggs laid. Results of these studies suggest that TCDD can be orally bioavailable from earthworms and crickets, important dietary sources for this species and other terrestrial species, as well as from nonfood items such as orally ingested soil and paper mill sludge solids.

For terrestrial mammals, the BCF value is the quotient of the concentration of CDD in the tissues divided by the concentration in food (Geyer et al. 1986a, 1986b). BCF values for 2,3,7,8-TCDD were calculated in the liver and/or fat of rats, cows, and monkeys (Geyer et al. 1986a; Kociba et al. 1978a). BCF values ranged from 10.9 to 24.5 in liver tissue and from 3.7 to 24.5 in fat tissue of rats fed 2,200, 210, or 22 ng/kg of 2,3,7,8-TCDD in their diet for 2 years (Geyer et al. 1986a; Kociba et al. 1978a). The BCF value calculated for this rat study, increased as the concentration in the animals' food decreased. In a cattle-feeding study, 24 ng 2,3,7,8-TCDD in the diet was fed to cows for 28 days after which time the BCF of 2,3,7,8-TCDD in the liver was 0.7 and in the fat was 3.5. Using a linear one compartment model, Geyer et al. (1986a) calculated that a steady state would be reached in 499 days and that the cattle fatty tissue would contain 594 ng/kg. The calculated BCF value for 2,3,7,8-TCDD would then be 24.8 (Geyer et al. 1986a; Jensen et al. 1981). This value is in good agreement with the BCF of 24.5 calculated for rats that received 22 ng TCDD/kg in their diet for years. This is a much higher BCF than has been reported by Fries and Paustenbach (1990). After 4 years of chronic exposure to 25 ng/kg 2,3,7,8-TCDD in their diet, the calculated BCF in fatty tissue of monkeys ranged from 24 to 40 (Geyer et al. 1986a). Using the 2,3,7,8-TCDD concentration in human adipose tissue (10.7 ppt whole weight) and in food (0.052–0.103 ng/kg), the calculated BCF is between 104 and 206 on a whole-weight basis, or between 115 and 229 on a lipid basis (90% lipid) (Geyer et al. 1986a). Using a pharmacokinetics model, the calculated BCF value is 153 (Geyer et al. 1986a). The authors further point out that the calculated BCFs for 2,3,7,8-TCDD in human adipose tissue are of the same order of magnitude as those calculated for PCBs, DDT, and hexachlorobenzene which are also persistent compounds with comparable lipophilicity (n-octanol/water partition coefficients). Based on this BCF range, 2,3,7,8-TCDD was ranked as having a

high bioconcentration potential in human adipose tissue (Geyer et al. 1986b). The half-life in humans was estimated to be approximately 7 years (Pirkle et al. 1989).

The primary mechanisms by which CDDs enter terrestrial food chains are by atmospheric wet and dry deposition of vapor-phase and particulate-bound chemicals (McCrady and Maggard 1993). Uptake of CDDs from soils by vegetables and other plants may occur (Schroll and Scheunert 1993). Accumulation of CDDs on vegetation may involve both of these mechanisms. Since 2,3,7,8-TCDD is lipophilic, adsorbs strongly to soil, and is not very soluble in water, root uptake and translocation to upper plant parts is only a minor source of vegetative contamination (Travis and Hattemer-Frey 1987) except perhaps for plant species belonging to the *Cucurbitaceas* (e.g., zucchini and pumpkin). For zucchini and pumpkin plants, root uptake of CDD/CDFs and subsequent translocation to the shoots and into the fruits is a main contamination pathway (Hulster et al. 1994). Hulster and Marschner (1993) reported that CDD levels in foliage were not related to CDD levels in soil. The contamination of plant foliage via atmospheric deposition is a more important contamination mechanism than root uptake and translocation to plant foliage (McCrady et al. 1990). Welschpausch et al. (1995) determined that dry deposition was the main pathway of uptake in grass of CDDs/CDFs from the atmosphere. Particles <2.9 μm in diameter were not important in atmospheric deposition, but large particles may contribute to HpCDD and OCDD accumulation. McCrady et al. (1990) conducted experiments with plants growing in nutrient solutions containing TCDD in a closed-laboratory system. These authors demonstrated that translocation from roots to shoots did not occur, but shoot contamination was associated with foliar uptake from the air. In general, there is little bioaccumulation of CDDs in plants (Hutzinger et al. 1985). BCFs for TCDD in plants have been estimated to be 0.0002, although most absorption occurs in the plant root with little or no translocation through the plant to the foliage (Wild and Jones 1992). A concentration of 0.06 ppm 2,3,7,8-TCDD was applied to the soil and root uptake from soil was then measured in oats and soybeans (Kearney et al. 1971). Oat and soybean plants (at all growth stages) accumulated very small quantities of 2,3,7,8-TCDD. A maximum of 0.15% (0.12 ppm) of 2,3,7,8-TCDD present in soils was translocated to the aerial portion of the oat and soybean plants. No detectable amounts of the compound were found in the oat or soybean plants harvested at maturity. The amount of 2,3,7,8-TCDD applied to these soils was many thousands of times greater than that which would occur in soils from herbicide applications containing a few ppm of 2,3,7,8-TCDD as an impurity. Even upon exposure to these high concentrations in the soil, significant amounts of 2,3,7,8-TCDD could not be measured in the plants (detection limit not reported) (Kearney et al. 1971).

Maize (corn) and bean cultivations grown in soils spiked with 22–1,066 ppt 2,3,7,8-TCDD showed 2,3,7,8-TCDD concentrations in roots ranging from 16 to 1,278 ppt for maize and from 37 to 1,807 for beans (Fachetti et al. 1986). The soil-grown crops did not show a significant increase of 2,3,7,8-TCDD in above-ground parts, either as a function of time or with increasing concentration of the pollutant in the soil (Fachetti et al. 1986).

Uptake of ^{14}C-labeled OCDD was studied in a closed, aerated-soil plant system for 7 days after application of the OCDD to soil (Schroll et al. 1994). The BCF (concentration of ^{14}C equivalent to the OCDD in plant dry matter divided by ^{14}C-labeled OCDD in dry soil) was 0.742 in carrot root and 0.085 in carrot shoots grown on OCDD-contaminated soil as compared to a BCF of not determinable and 0.084 in the control carrot root and shoots, respectively. There was no transport of ^{14}C-labeled OCDD between the roots and shoots or vice versa. The residues in roots were due only to root uptake from the soil; those in shoots were due only to foliar uptake from the air.

Muller et al. (1993) studied transfer pathways of CDD/CDFs to fruit. These authors found that homologue patterns of CDDs/CDFs in soil were different from those in both apples and pears grown in the contaminated soil. Concentrations of CDDs/CDFs ranged from 1 to 4 ng/kg (fresh weight) and were 4–8 times higher in the peel than in the pulp. These authors suggest that airborne CDDs/CDFs are a major source of contamination of fruits grown in contaminated soil. Muller et al. (1994) conducted field studies of CDD transfer pathways from soil to several edible plant varieties (carrots, lettuce, and peas). Plants were grown in soil with 5 ng TEQ/kg or total CDD/CDF concentrations of 363 ng/kg dry weight (control plots) and 56 ng TEQ/kg or total CDD/CDF concentrations of 3,223 ng/kg dry weight on the contaminated plots. CDD/CDF concentrations in carrot peels were three times higher on the contaminated plots than on the control plots. This was the result of a 10-fold increase in the CDD/CDF levels in the carrot peel. CDD/CDF concentrations in lettuce (17.7 and 21.1 ng/kg dry weight) and in peas (7.1 ng/kg dry weight) were not any higher when grown on the contaminated plot as compared to the control plots and were much lower than concentrations in the carrots (47.3 and 47.5 ng/kg, dry weight). This indicates that the CDD/CDFs in the lettuce and peas from both plots were of atmospheric origin. The CDD/CDF homologue pattern in the contaminated soil showed OCDFs and HpCDFs were the two most prevalent congeners, while the CDD/CDF homologue pattern from the peel of carrots grown on the contaminated plots contained TCDF, PeCDF, and HxCDF. Levels of TCDD were the lowest of all CDD/CDF homologues in both contaminated soils and carrot peels. The homologue profile in lettuce samples was largely dominated by lower chlorinated CDFs (TCDF and PeCDF) and higher chlorinated CDDs (HpCDD and OCDD), a

profile often found in samples of atmospheric deposition (Eitzer and Hites 1989a, 1989b). The lowest CDD/CDF levels of this study were found in peas with pea pods showing higher levels than seeds. The homologue profiles was dominated by lower chlorinated CDFs and higher chlorinated CDDs similar to the profile found in lettuce.

Since most of the CDDs released into the atmosphere settle onto water and soil surfaces, foliar deposition is the major route of vegetative contamination (Travis and Hattemer-Frey 1987). The translocation of foliar-applied 2,3,7,8-TCDD has been studied (Kearney et al. 1971). Labeled 2,3,7,8-TCDD was applied to the center leaflet of the first trifoliate leaf of 3-week-old soybean plants and the first leaf blade of 12-day-old oat plants. The compound was applied in an aqueous surfactant solution to enhance leaf adsorption and to keep the water-insoluble TCDD in solution. Plants were harvested 2, 7, 14, and 21 days after treatment, dissected into treated and untreated parts, and analyzed. 2,3,7,8-TCDD was not translocated from the treated leaf to other plant parts. Very little 2,3,7,8-TCDD was lost from soybean leaves, while a gradual loss (38% in 21 days) did occur from oat leaves (Kearney et al. 1971). The authors considered volatilization to be a possible mechanism for removal of 2,3,7,8-TCDD, but photolysis may also have contributed to the loss.

McCrady and Maggard (1993) measured the uptake and elimination mechanisms for 2,3,7,8-TCDD applied to grass foliage in a closed-laboratory system using [^{3}H]TCDD. The [^{3}H]2,3,7,8-TCDD was injected into the chamber as a vapor originating from a [^{3}H]2,3,7,8-TCDD generator. The total recovered radioactivity was 74%. Plant foliage accounted for 59% and the air and other chamber components accounted for 6 and 9%, respectively. This indicated that plant foliage was a major sink for [^{3}H]2,3,7,8-TCDD vapor. Less than 0.2% was recovered from the soil and associated with root tissues, further verifying an airborne mechanism of [^{3}H]2,3,7,8-TCDD uptake and negligible translocation. The authors also demonstrated that both photodegradation and volatilization were primary loss mechanisms for [^{3}H]2,3,7,8-TCDD. The photodegradation half-life (first-order kinetics) of 2,3,7,8-TCDD sorbed to grass and exposed to natural sunlight was 44 hours, while the half-life for volatilization of 2,3,7,8-TCDD from grass foliage was 128 hours.

In conclusion, CDDs may be transported long distances in the atmosphere. They eventually may be deposited on soils or surface water as a result of wet or dry deposition. CDDs will slowly volatilize from the water column or, more likely, will adsorb to suspended particulate materials in the water column and be transported to the sediment. CDDs deposited on soils will strongly adsorb to organic matter. They are

unlikely to leach to underlying groundwater, but may enter the atmosphere on soil or dust particles or enter surface water in runoff. Low water solubilities and high lipophilicity indicate that CDDs will bioconcentrate in aquatic organisms, although as a result of their binding to suspended organic matter, actual uptake by these organisms may be less than predicted. This is also true of uptake and bioconcentration by plants, although foliar deposition and adherence may be significant.

5.3.2 Transformation and Degradation

CDDs belong to a class of highly lipophilic compounds with low water solubility and low chemical reactivity that are resistant to microbial degradation. The dominant transformation processes affecting their fate have been shown to be surface photolysis and gas-phase diffusion/volatilization with subsequent photolysis (Yanders et al. 1989).

5.3.2.1 Air

The primary transformation reaction for CDDs in the atmosphere depends on whether the CDD is in the vapor or particulate phase. Vapor-phase CDDs are not likely to undergo reactions with atmospheric ozone, nitrate, or hydroperoxy radicals; however, reactions with hydroxyl radicals may be significant, particularly for the less-chlorinated congeners (MCDD through TCDD) (Atkinson 1991). Based on the photolysis lifetimes of CDDs in solution, it is expected that vapor-phase CDDs will also undergo photolysis in the atmosphere, although reactions with hydroxyl radicals will predominate. For TCDD, the photolytic lifetime ranges from 1.3 to 7.1 days, depending on the season (faster in summer), whereas the hydroxyl radical reaction lifetime is estimated to be 2 days (Atkinson 1991). A half-life of 8.3 days was estimated for the gas-phase reaction of 2,3,7,8-TCDD with photochemically produced hydroxyl radicals in the atmosphere (Podoll et al. 1986). Using the gas-phase hydroxyl radical reaction rate constant of 1×10^{-11} cm^3-$molecule^{-1}$ sec^{-1} and an average 12-hour daytime hydroxyl radical concentration of 1.5×10^6 molecules cm^{-3}, the atmospheric lifetimes of CDDs are estimated to range from 0.5 days for MCDD to 9.6 days for OCDD, with TCDD having a lifetime of 0.8–2 days (Atkinson 1991).

Particulate-bound CDDs are removed by wet or dry deposition with an atmospheric lifetime $10 days (Atkinson 1991) and, to a lesser extent, by photolysis. Miller et al. (1987) measured photolysis of 2,3,7,8-TCDD sorbed onto small-diameter fly ash particulates suspended in air. The results indicated that fly ash confers photostability to the adsorbed 2,3,7,8-TCDD. The authors reported little (8%) to no loss of

2,3,7,8-TCDD on the fly ash samples after 40 hours of illumination in simulated sunlight. Koester and Hites (1992) studied the photodegradation of CDDs naturally adsorbed to five fly ash samples (two from coal-fired plants, two from municipal incinerators, and one from a hospital incinerator). Although the authors reported that CDDs underwent photolysis in solution and on silica gel, no significant degradation was observed in 11 photodegradation experiments conducted for periods ranging from 2 to 6 days.

The selected transformation of the more and less chlorinated CDDs has been demonstrated by the analysis of CDDs found in soil samples compared with atmospheric concentrations of CDDs at the emission source (Marklund et al. 1991; Yamamoto and Fukushima 1993). Soil samples contained progressively greater concentrations of HpCDD and OCDD with increasing distance from the emission source, indicating that photolysis of the less chlorinated congeners was occurring (Eitzer 1993). In the air, the low vapor pressure of OCDD results in its partitioning primarily to the particulate phase rather than the vapor phase; therefore, atmospheric photodegradation is less likely to occur for this tightly bound congener (Eitzer 1993).

5.3.2.2 Water

Photolysis is the major route of CDD disappearance in aqueous solutions (Hutzinger et al. 1985). While photolysis is a relatively slow process in water, CDDs are rapidly photolyzed under certain conditions, (i.e., when exposed to ultraviolet light of the appropriate wavelength and in the presence of an organic hydrogen donor). These hydrogen donors can be expected to be present in chlorophenol pesticides either as formulation solvents (e.g., xylene or petroleum hydrocarbons), as active constituents of the formulation (e.g., the alkyl esters of 2,4-D and 2,4,5-T), or as natural organic films on soils (Crosby et al. 1973). The photolytic behavior of CDDs in an organic solvent or in a water-organic solvent, however, may not accurately reflect the photolytic behavior of these compounds in natural waters (Hutzinger et al. 1985). For example, Choudry and Webster (1989) reported that photolysis of 1,3,6,8-TCDD was slower in natural pond-water solutions than was predicted from studies with laboratory solutions. Conversely, Friesen et al. (1990) reported that photolysis of PeCDD and HpCDD proceeds faster in a pond or lake-water solutions than was predicted or measured in a laboratory solution. In general, however, lower chlorinated CDDs are degraded faster than higher chlorinated congeners. Chlorine atoms in the lateral positions (e.g., 2, 3, 7, 8) are also more susceptible to photolysis than are chlorine atoms in the para positions (e.g., 1, 4, 6, 9) (Choudhry and Hutzinger 1982; Crosby et al. 1973; Hutzinger et al. 1985).

Podoll et al. (1986) used the quantum yield data of Dulin et al. (1986) for a water:acetonitrile solution to calculate seasonal half-life values for dissolved 2,3,7,8-TCDD at 40 degrees north latitude in clear near-surface waters. Photolysis half-lives for dissolved 2,3,7,8-TCDD in sunlight range from 118 hours in winter, to 51 hours in fall, to 27 hours in spring, to 21 hours in summer (Podoll et al. 1986). Choudhry and Webster (1989) studied photolysis of a series of CDDs in a water:acetonitrile solution (2:1 v/v). These authors estimated the midday midsummer sunlight photolysis half-lives values at 40 degrees north latitude in clear near-surface waters as follows: 1,3,6,8-TCDD (0.3 days), 1,2,3,7-TCDD (1.8 days), 1,2,3,4,7-PeCDD (15 days), 1,2,3,4,7,8-HxCDD (6.3 days), 1,2,3,4,6,7,8-HpCDD (47 days), and OCDD (18 days) near the surface of water bodies (Choudhry and Webster 1989). Sunlight photolysis half-lives were also reported for the spring, fall, and winter for 1,2,3,4,6,7,8-HpCDD (57, 88, and 156 days, respectively) and for OCDD (21, 31, and 50 days, respectively) (Choudhry and Webster 1989). Photolysis half-lives for 1,2,3,4,6,7,8-HpCDD and OCDD in water-acetonitrile solutions irradiated at 313 nm were reported to be 8 and 7.7 days, respectively (Choudhry and Webster 1987, 1989). The half-lives of 1,3,6,8-TCDD and OCDD in lake water are 2.6 and 4 days, respectively, with removal by partitioning to the lake sediments (Servos et al. 1992).

The photodegradation profiles of 2,3,7,8-TCDD, 1,3,6,8-TCDD, and 1,2,3,4-TCDD in 1,4-dioxane solutions at various wavelengths under xenon lamp irradiation were studied (Koshioka et al. 1989a, 1989b, 1989c). Reductive dechlorination reactions were observed in the photolysis of TCDD isomers. After 200 minutes of irradiation with a xenon lamp, 2,3,7,8-TCDD formed 2,3,7-TrCDD, 2,7-DCDD, 2,8-DCDD, 2-MCDD, and DD. Photodegradation half-lives of 2,3,7,8-TCDD at the maximal photodegradation wavelengths of 252.6 nm and 318.6 nm were 72.6 minutes and 29.7 minutes, respectively (Koshioka et al. 1989b, 1989c). After 267 minutes of irradiation with a xenon lamp, 1,3,6,8-TCDD formed 1,3,6-TrCDD, 1,3-DCDD, 1,6-DCDD, 1-MCDD, 2-MCDD, and DD, while 1,2,3,4-TCDD formed 1,2,3-TrCDD, 1,2,4-TrCDD, 1,2-DCDD, 1,3-DCDD, 1,4-DCDD, 2,3-DCDD, 1-MCDD, 2-MCDD, and DD (Koshioka et al. 1989a).

The photolytic half-life of 2,3,7,8-TCDD in isooctane was estimated to be 40 minutes with a light source at 0.5 meters and 3 hours with a light source at 1 meter (Stehl et al. 1973). Very little change was observed in OCDD on exposure to artificial sunlight. Approximately 20% photolysis of OCDD was observed in isooctane at the end of 18 hours and about 6% photolysis of OCDD after 20 hours of exposure in 1-octanol (Stehl et al. 1973). Irradiation of pentachlorophenol (PCP) dissolved in sodium hydroxide at a wavelength

of 300 nm (equivalent to sunlight) for 16 hours produced OCDD (Crosby and Wong 1976). OCDD then underwent photoreduction to HpCDD as a PCP photolysis product (Crosby and Wong 1976).

Under equivalent light exposure conditions, photolytic half-lives were determined for each of the individual TCDD isomers in dilute hydrocarbon solution and as a diffuse molecular dispersion on a clean soft-glass surface (Nestrick et al. 1980). The photolytic behavior of 2,3,7,8-TCDD was atypical compared to other TCDD isomers. In a hydrocarbon solution, 2,3,7,8-TCDD had the fastest decomposition rate (half-life 56.8 minutes) and 1,4,6,9-TCDD had the slowest decomposition rate (half-life 8,400 minutes [5.8 days]). The half-lives of the remaining TCDD isomers ranged from 153 to 1,388 minutes (2.55–23.1 hours). However, as a diffuse molecular dispersion on a glass surface, the 2,3,7,8-TCDD had the slowest decomposition rate (half-life 8,400 minutes [5.8 days]), and 1,4,6,9-TCDD had the second slowest decomposition rate (half-life 830 minutes [13.8 hours]). The half-lives of the remaining TCDDs ranged from 121 to 560 minutes (2–9.3 hours). The majority of TCDD isomers photolytically decomposed faster on a glass surface than in a hydrocarbon solution under conditions of equivalent light intensity. 2,3,7,8-TCDD and 1,4,6,9-TCDD possess the highest degree of symmetry within the group, and these isomers demonstrated the largest change in the photodecomposition rate for surface and solution reactions, with the changes being in opposite directions. Additional photolysis tests were conducted using more highly chlorinated CDD congeners. In a hydrocarbon solution, the half-lives of 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,9-HpCDD, and OCDD were 1,800 minutes (1.3 days), 3,300 minutes (2.3 days), and 1,460 minutes (1.01 days), respectively, and 3,140 minutes (2.18 days), 2,400 minutes (1.67 days), and 48,900 minutes (33.96 days), respectively, on a glass surface (Nestrick et al. 1980).

2,3,7,8-TCDD decomposed rapidly when dissolved in methanol and exposed to ultraviolet (UV) light (Plimmer et al. 1973). Rate measurements showed that 2,3,7,8-TCDD is more rapidly photolyzed in methanol than OCDD (Plimmer et al. 1973). The photolysis half-lives for 2,3,7,8-TCDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,9-HpCDD, and OCDD in *n*-hexadecane solution were 56.8 minutes, 1,800 minutes (1.25 days), 3,300 minutes (2.29 days), and 1,460 minutes (1.01 days), respectively (Mamantov 1984).

Solution-phase photolysis of HpCDD and OCDD has been reported (Dobbs and Grant 1979). Solutions of these CDDs in hexane (approximately 1 µg/mL) were exposed to natural sunlight as well as to fluorescent blacklight. The photolytic half-life for OCDD exposed to both types of radiation was 16 hours. HpCDD was generated by photolysis of OCDD (Dobbs and Grant 1979). The photolytic half-lives of

1,2,3,4,6,7,9-HpCDD and 1,2,3,4,6,7,8-HpCDD were 28 hours and 11 hours, respectively (Dobbs and Grant 1979).

It has been suggested that the potential for biological degradation of 2,3,7,8-TCDD in a wide variety of environmental samples is low (Arthur and Frea 1989). The fate of 2,3,7,8-TCDD in sediment and water from two lakes in Wisconsin was examined (Ward and Matsumura 1978). After incubation periods of up to 589 days, little metabolism of 2,3,7,8-TCDD was detected. The slight metabolism that was detected was stimulated by the presence of sediment and the addition of nutrients (Ward and Matsumura 1978). Also, 2,3,7,8-TCDD does not hydrolyze in water (Mabey et al. 1982; Miller et al. 1987).

5.3.2.3 Sediment and Soil

Photolysis of 2,3,7,8-TCDD on soils is a relatively slow process compared to photolysis in an aqueous media (Kieatiwong et al. 1990). 2,3,7,8-TCDD applied to soil or a solid surface seems to be extremely resistant to the action of sunlight and decomposes very slowly (Plimmer et al. 1973). A methanol solution of 2,3,7,8-TCDD (2.4 ppm) applied to glass plates coated with soil and illuminated 96 hours with a fluorescent UV lamp remained unchanged at the end of the period (Plimmer et al. 1973). Organic solvents added to the soil, however, can enhance the extent of photolysis. Use of a solvent mixture of tetradecane and 1-butanol to TCDD-treated soil, combined with exposure to sunlight, resulted in 61–85% photodegradation of TCDD after 60 days. The solvent was effective in transporting TCDD from deeper in the soil column (60 cm) to the soil surface via evaporation. At the soil surface, photodegradation could occur. TCDD concentrations at 60 cm decreased from 23.8 ng/g (ppb) to 7.1 ng/g (ppb) after 60 days (McPeters and Overcash 1993).

Photolysis of OCDD (10 mg/kg) on soils resulted in production of the lower chlorinated CDDs, notably 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, three HxCDD isomers substituted at the 2,3,7,8-positions, and 1,2,3,4,6,7,8-HpCDD. Photolysis of OCDD occurred in mean soil depths between 0.06 and 0.13 mm (Miller et al. 1989). Approximately 30–45% of OCDD was lost by day 5 of irradiation; no further significant loss of OCDD was observed following 10 additional days of irradiation. Although photolysis only occurred at shallow soil depths and the conversion of OCDD to the more toxic TCDD, PeCDD, and HxCDD homologues was small (0.5–1%) compared with the photodechlorination to HpCDD (67%), photolysis of OCDD may represent a significant source of these toxic isomers (Miller et al. 1989).

The loss of 2,3,7,8-TCDD in contaminated soil has been studied under natural conditions in experimental plots at the Dioxin Research Facility, Times Beach, Missouri (Yanders et al. 1989). The 2,3,7,8-TCDD concentration profiles of sample cores taken at Times Beach in 1988 were virtually the same as those in cores taken in 1984. The authors concluded that the loss of 2,3,7,8-TCDD due to photolysis at Times Beach was minimal in the 4 years covered by the study (Yanders et al. 1989). Estimates of the half-life of TCDD on the soil surface range from 9 to 15 years, whereas the half-life in subsurface soil may range from 25 to 100 years (Paustenbach et al. 1992).

A white rot fungus *(Phanerochaete chrysosporium)* has demonstrated the ability to degrade 2,3,7,8-TCDD in laboratory experiments (Bumpus et al. 1985; Des Rosiers 1986). In cultures containing 1.25 nmol of the 2,3,7,8-TCDD substrate, 27.9 pmol were mineralized to CO_2 in 30 days (2.23% metabolism) increasing to 49.5 pmol in 60 days (3.96% metabolism) (Des Rosiers 1986). It was suggested that the ability of this fungus to metabolize 2,3,7,8-TCDD is dependent on its extracellular lignin-degrading enzyme system (Bumpus et al. 1985; Des Rosiers 1986). More recently, Valli et al. (1992) reported that 2,7-DCDD also was degraded by *P. chrysosporium* via the removal of both aromatic chlorines before aromatic ring cleavage took place.

Cultures of *Pseudomonas testosteroni*, of an unidentified bacterium isolated from soil from Seveso, Italy, and of a mixture of 6 unidentified bacterial strains isolated from Seveso soil were incubated aerobically with ^{14}C-2,3,7,8-TCDD for 35, 54, and 12 weeks, respectively (Philippi et al. 1982). Results showed the occurrence of a metabolite of ^{14}C-2,3,7,8-TCDD in all three cultures. The polar metabolite amounted to approximately 1% of the input material and was found to be a hydroxylated derivative of ^{14}C-2,3,7,8-TCDD (Philippi et al. 1982).

Approximately 100 strains of pesticide-degrading microorganisms were tested for their ability to degrade 2,3,7,8-TCDD (Matsumura and Benezet 1973). The organisms were maintained in liquid axenic culture, and the production of metabolites from ring-labeled ^{14}C-2,3,7,8-TCDD was measured. Five strains were identified that showed some ability to degrade ^{14}C-2,3,7,8-TCDD. The degradative organisms included a fungus *(Trichoderma viride)*, a bacterium *(Pseudomonas putida)*, and three organisms referred to by coded numbers (Matsumura and Benezet 1973).

To determine the persistence of 2,3,7,8-TCDD, concentrations of 1, 10, and 100 ppm of unlabeled 2,3,7,8-TCDD were added to 300-g samples of silty loam and sandy soils and then assayed periodically for

residues (Kearney et al. 1971). Measurements of 2,3,7,8-TCDD residues after 20, 40, 80, 160, and 350 days of incubation at 28 EC in foil-sealed beakers indicated a relatively slow degradation process in both soils. After 350 days, 56% of the initially applied 2,3,7,8-TCDD was recovered from the sandy soil, while 63% was recovered from the silty clay loam for all concentrations (Kearney et al. 1971).

Parsons (1992) studied the influence of suspended sediment on the biodegradation of several CDDs. In this study, aqueous solutions of a mixture of 2-chloro-, 1,3-dichloro, 2,8-dichloro-, and 1,2,4-trichloro CDDs were incubated for 24 days with 100 mg/L suspended sediment. Subsequently, the degradation of the CDDs in the sediment suspensions by *Alcaligenes sp.* strain JB1 was compared to that in solutions without sediment. The amounts of all four CDD compounds degraded in the sediment suspensions after 7 days were greater than those initially present in the dissolved phase, based on their calculated sediment-water partition coefficients. The sorbed fractions were, therefore, sufficiently desorbed to be partly degraded. However, the biodegradation rates were slower in the sediment suspensions than in the solutions. The results indicate that sorbed fractions of CDDs formed after relatively short incubation periods are sufficiently labile to be available for biodegradation after desorption. Evidence that the presence of sediment lowers biodegradation rates in sediment suspension, however, implies that longer residence times, such as those observed under field conditions, may also lead to a significant lowering of the biodegradation rates in soil. This will apply even more to the more highly chlorinated CDD congeners. In another study, the degradation of highly chlorinated CDD congeners (5–7 chlorine/molecule) was studied for a period of 6 months in anaerobic microcosm incubations using PCB-contaminated Hudson River sediments and creosote-contaminated aquifer samples from Pensacola, Florida (Adriaens and Grbic-Galic 1994). The authors reported (pseudo-first-order) half-life values for 1,2,3,4,6,7,8-HpCDD of 4.1 and 2.9 years for the Hudson River and Pensacola aquifer-incubated microcosm samples, respectively. The half-life values for 1,2,3,4,7,8-HxCDD were 2 and 2.9 years for the Hudson River and Pensacola aquifer-incubated microcosm samples, respectively. The 1,2,4,6,8,9/ 1,2,4,6,7,9-HxCDD congeners were found not to be degraded, which was presumably due to the low concentration spiked. The authors reported that tentative identification of the degradation products indicate that para-dechlorination was the preferential route of reduction, as has been observed with 1,2,3,4,5,6,7,8-HpCDD in aquifer microcosms. This observation is contrary to photolytic dechlorination patterns of soil-sorbed CDDs.

Beurskens et al. (1995) reported that an anaerobic microbial consortium enriched from Rhine River sediments was able to remove chlorine substituents from CDDs. A model CDD, 1,2,3,4-TCDD, was reductively dechlorinated to both 1,2,3- and 1,2,4-TrCDD. These TrCDD compounds were further

dechlorinated to 1,3- and 2,3- DCDD and trace amounts of 2-MCDD. The TrCDD compounds were detected at low concentrations, but the 1,3- and 2,3- DCDD were detected at higher concentrations. The anaerobic culture dechlorinates 1,2,3,4-TCDD at a relatively rapid rate with a half-life value estimated at 15.5 days (first-order kinetics). The formation of metabolites with a conserved 2,3-substitution pattern from 1,2,3,4-TCDD indicates that dechlorination of highly chlorinated CDDs may result in metabolites that are potentially more toxic than the parent compounds.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to CDDs depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Historically, CDD analysis has been both complicated and expensive, and the analytical capabilities to conduct such analysis have been available through only a relatively few analytical laboratories. Limits of detection have improved greatly over the past decade with the use of high-resolution mass spectrometry, improvements in materials used in sample clean-up procedures, and with the use of known labeled and unlabeled chemical standards. Problems associated with chemical analysis procedures of CDDs in various media are discussed in greater detail in Chapter 6. In reviewing data on CDD levels monitored or estimated in the environment, it should be noted that the amount of the chemical identified analytically is not necessarily equivalent to the amount that is bioavailable (see Section 2.3) and that every measurement is accompanied with a certain analytical error.

5.4.1 Air

Indoor household dust samples gathered by a vacuum cleaner from rooms with furniture treated with a wood-preserving formulation were analyzed for CDDs (Christmann et al. 1989b). The wood-preserving formulation contained PCP, which is known to be contaminated with CDDs, particularly HxCDD, HpCDD, and OCDD. OCDD was the most abundant congener found in the dust samples at an average concentration of 191 µg/kg (ppb), followed by HpCDD (20 µg/kg), HxCDD (2.5 µg/kg), PeCDD (0.9 µg/kg), and TCDD (0.2 µg/kg) (Christmann et al. 1989b).

Indoor air concentrations of CDD/CDFs were measured in kindergarten classrooms in West Germany to evaluate releases from wood preservatives (e.g., PCP) that may have been used in building materials (Päpke et al. 1989a). Measured indoor air concentrations of total CDD/CDF ranged from 1.46 to

4.27 pg/m^3, while measured outdoor air concentrations ranged from 0.61 to 78.97 pg/m^3. The 2,3,7,8-substituted congeners predominated with mean concentrations as follows: OCDD (131.5 pg/m^3), 1,2,3,4,6,7,8-HpCDD (77 pg/m^3), 1,2,3,4,6,7,8-HpCDF (51 pg/m^3), and OCDF (25.3 pg/m^3).

Measured indoor air samples collected in an office building in Binghamton, New York, 2 years after a fire in an electrical transformer that contained PCBs and tri- and tetra-chlorobenzenes had concentrations of 2,3,7,8-TCDD ranging from 0.23 to 0.47 pg/m^3 (0.017–0.036 ppq) (Smith et al. 1986a). The 2,3,7,8-TCDD isomer constituted 23–30% of the 1.0–1.3 pg/m^3 (0.076–0.099 ppq) total TCDDs. The limit of detection for these samples was approximately 0.003 pg/m^3 (Smith et al. 1986a).

Background levels of CDD in air were measured in a semi-rural location in Elk River, Minnesota, located about 25 miles northwest of Minneapolis-St. Paul (Reed et al. 1990). No major industrial or commercial activity occurred in the area at the time of the study. Ambient air samples were collected in the winter and summer of 1988. 2,3,7,8-TCDD was not detected in any of the ambient air samples taken in the summer (detection limits for 2,3,7,8-TCDD ranged from 0.005 to 0.065 pg/m^3 [0.0004–0.0046 ppq]). 2,3,7,8-TCDD was noted in a wintertime sample at concentrations of 0.015 pg/m^3 (0.0011 ppq) and 0.019 pg/m^3 (0.0014 ppq). Detection limits in the remaining wintertime samples for 2,3,7,8-TCDD ranged from 0.005 to 0.01 pg/m^3 (0.0004–0.0007 ppq). Wintertime CDD concentrations were greater than those observed for summertime. The authors noted that this may be a result of increased numbers of combustion sources operating during the winter months. The wintertime CDD congener profile showed increasing concentrations with increasing chlorine substitutions. Average wintertime ambient air concentrations of HpCDD and OCDD ranged from approximately 0.5 to 4.1 pg/m^3 (0.029–0.236 ppq) and 0.74 to 8.2 pg/m^3 (0.039–0.436 ppq), respectively (Reed et al. 1990). Average summertime ambient air concentrations of HpCDD and OCDD ranged from approximately 0.204 to 0.246 pg/m^3 (0.011–0.014 ppq) and 0.018 to 0.024 pg/m^3 (0.001–0.0013 ppq), respectively (Reed et al. 1990). The authors found that, in general, the more highly chlorinated congeners were present at higher concentrations that the less chlorinated congeners.

A long-term study (1985–1988) of CDDs in the ambient atmosphere of Bloomington, IN (a suburban area), was carried out in order to provide base-line data against which the impact of a future incinerator on local CDD concentrations could be judged (Eitzer and Hites 1989b). Ambient air samples were analyzed for the presence of CDDs in both the particulate-bound phase and the vapor-phase forms. At the four sites sampled, the concentrations of CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) increased with an increasing level of chlorination. All sites showed that the less chlorinated CDDs have a higher vapor-phase

fraction than the more chlorinated CDDs. In addition, all sites show OCDD to be the most abundant CDD, averaging from 0.44 to 0.69 pg/m^3 (0.023–0.032 ppq) (detection limit 0.001 pg/m^3 [5.3×10^{-5} ppq]) (Eitzer and Hites 1989b). A seasonal effect was seen on the proportion of the total atmospheric burden present in the vapor phase. During the warm summer months, the total vapor-to-particle bound ratio (V/P) was as great as 2, whereas in the winter it was <0.5. At warm temperatures, most of the less chlorinated CDDs are found in the vapor phase, whereas at cooler temperatures more of the CDDs were associated with the particle phase (Eitzer and Hites 1989b).

CDDs have been found in urban air particulates from Washington, D.C., and St. Louis, Missouri; OCDD was the predominant congener at concentrations of 200 ppb and 170 ppb for Washington and St. Louis, respectively (Czuczwa and Hites 1986a). Combustion of municipal and chemical wastes was the most likely source of these compounds. CDDs were detected in air samples from Albany, Binghamton, Utica, and Niagara Falls, NY (Smith et al. 1990b). Concentrations of CDD congener groups for all 4 cities were as follows: total TCDD, not detected (<0.21 pg/m^3 [0.016 ppq]); total PeCDD, <0.04–0.62 pg/m^3 (<0.003–0.043 ppq); total HxCDD, 0.10–2.4 pg/m^3 (0.007–0.15 ppq); total HpCDD, <0.21–4.4 pg/m^3 (0.012–0.25 ppq); and OCDD <0.54–4.6 pg/m^3 (0.029–0.244 ppq) (Smith et al. 1990b). In 1988–89, total CDDs measured downwind from an industrial source in Niagara Falls, NY, ranged from 0.3 pg/m^3 to 133 pg/m^3 and were approximately 2.5 times higher than upwind concentrations (Smith et al. 1990b). Between 1986 and 1990, total CDD concentrations averaged 2.3 pg/m^3, of which 65% was OCDD (Smith et al. 1992).

An extensive multi-year monitoring program for CDDs/CDFs was conducted at eight sampling locations in the Los Angeles South Coast Air Basin from 1987 to 1989 (Hunt and Maisel 1992). The monitoring network, which monitored for both vapor and particulates, included several sites situated in residential areas as well as sites in the vicinity of suspected CDD/CDF sources. Monitoring results indicated that 2,3,7,8-TCDD was virtually undetected. The most commonly detected 2,3,7,8-substituted congener was OCDD followed by 1,2,3,4,6,7,8-HpCDD. The predominance of 1,2,3,4,6,7,8-HpCDD as the most persistent congener is associated with stationary or mobile combustion source emissions. 1,2,3,4,6,7,8-HpCDD was found at all 7 sampling sessions at a mean concentration of 1.140 pg/m^3. OCDD also was found at all 7 sampling sessions at a mean concentration of 2.883 pg/m^3. The mean total TCDD concentration was 0.114 pg/m^3 and was measured during only 3 sampling sessions (Hunt and Maisel 1992).

The concentrations of CDDs in the ambient air at several sites in metropolitan Dayton, Ohio, have been determined (Tiernan et al. 1989b). No CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) were found in rural regions, with average detection limits ranging from 0.03 pg/m^3 (TCDD) to 1.44 pg/m^3 (OCDD). The rural area was outside the impact zone of air pollutants from any regional industrial sources. CDDs in the industrialized regions appear to originate from a combination of sources, including municipal waste incinerators, motorized vehicles, and a PVC-coated metal incinerator, the latter being a major source of these pollutants. Suburban/roadside area samples were taken at ground level at a distance of about 3 meters from a street intersection through which approximately 60,000 cars passed each day. Other sampling sources were on the roofs of buildings in the downtown Dayton area, which lay in the emissions path from municipal solid-waste incinerators. TCDDs and PeCDDs (detection limits 0.01 and 0.03 pg/m^3, respectively) were not detected in the suburban/roadside area but were detected in the municipal waste-incinerator areas at 0.24 and 0.38 pg/m^3, respectively. HpCDD was detected in both the suburban/roadside areas and the municipal waste-incinerator areas at concentrations of 0.41 pg/m^3 (0.024 ppq) and 3.34 pg/m^3 (0.19 ppq), respectively. OCDD was also detected in the suburban/roadside areas (1.09 pg/m^3 [0.058 ppq]) and the municipal waste incinerator areas (4.69 pg/m^3 [0.25 ppq]). Concentrations of HxCDD were lower than HpCDD and OCDD, 0.05 pg/m^3 (0.003 ppq) in the suburban/ roadside areas and 2.56 pg/m^3 (0.160 ppq) in the vicinity of the municipal waste incinerators (Tiernan et al. 1989b).

Air samples were collected in Ohio in 1987 at an industrial area, an urban area downwind of a municipal incinerator, a high-traffic density area, and a rural area (Edgerton et al. 1989). No 2,3,7,8-TCDD was detected in any of the air samples with detection limits of <0.24 pg/m^3 (0.02 ppq) in any of the areas. The ambient concentrations of CDDs collected in the urban area were as follows: total HpCDD, 1.0–1.1 pg/m^3 (0.058–0.063 ppq); OCDD, 1.0–1.2 pg/m^3 (0.053–0.064 ppq); PeCDD, 0.1 pg/m^3 (0.03 pg/m^3); and total HxCDD, 0.6–0.63 pg/m^3 (0.038–0.039 ppq) (detection limit not specified). Concentrations of CDDs in the industrial area were: total HpCDD, 0.41–1.0 pg/m^3 (0.024–0.058 ppq), OCDD, 0.51–1.1 pg/m^3 (0.027–0.058 ppq), and total HxCDD, 0.43–0.78 pg/m^3 (0.027–0.049 ppq). Concentrations of total HpCDD, OCDD, total HxCDD in the high-traffic density area were 0.56 pg/m^3 (0.032 ppq), 0.96 pg/m^3 (0.051 ppq), and 0.15 pg/m^3 (0.008 ppq), respectively. Ambient air concentrations of total HpCDD, OCDD, and total HxCDD in the rural area were 0.48 pg/m^3 (0.028 ppq), 0.5 pg/m^3 (0.027 ppq), and 0.33 pg/m^3 (0.021 ppq), respectively. PeCDD was not detected in the industrial, high-traffic, or rural areas (Edgerton et al. 1989).

Air monitoring at Windsor, Ontario, downwind of a proposed municipal solid-waste incinerator in Detroit, Michigan, between 1987 and 1988 found a mean total CDD concentration of 2.12 pg/m^3. A sampling station located in a rural area 30 miles away provided background total CDD concentrations of 0.51 mg/m^3. At both stations, the primary congeners were HpCDD and OCDD in the particulate phase, whereas TCDD and PeCDD were not detected in the vapor or particulate phases above the detection limit (Bobet et al. 1990).

A mixture of CDDs (TCDD, PeCDD, HxCDD, HpCDD, OCDD) has been found in emissions from the combustion of various sources, including municipal incinerators, power plants, wood burning, house-heating systems, and petroleum-refining operations (Chiu et al. 1983; Clement et al. 1985; Thoma 1988; Thompson et al. 1990). CDDs were found in stack and fly ash samples from the following combustion sources (ranges given): municipal incinerator, 8 ppb (OCDD) to 390 ppb (HxCDD) (TCDD was found at 10 ppb); open-air burning of PCP-treated wood, 2 ppb (TCDD) to 187 ppb (OCDD); coal-fired power plant, 1 ppb (TCDD) to 6 ppb (PeCDD and HxCDD); hydroelectric power plant, 0.5 ppb (OCDD) to 5.2 ppb (TCDD) (Chiu et al. 1983); and petroleum refining, 0.8 (OCDD) to 3.4 ng/m^3 (PeCDD) (Thompson et al. 1990). Samples of ash from wood-burning stoves, a fireplace, and open-air wood burning contained detectable levels of CDDs ranging from 0.3 to 33 ppb (Clement et al. 1985). The open-air burning ash contained the highest total CDD concentration (33 ppb), with HpCDD being the most abundant homologue (11 ppb). The total CDD concentrations in 4 samples from wood-burning stoves ranged from 0.3 to 15 ppb, with the relative amounts of each homologue varying for each sample. Ash samples from the fireplace contained total CDD concentrations ranging from 3.1 to 5.4 ppb, with HxCDD (0.3–1.7 ppb) and OCDD (0.4–3.1 ppb) being the most abundant homologues present (Clement et al. 1985). TCDD was present in ash samples from open-air burning (0.8 ppb) and was detected in ash from the fireplace.

Ambient air monitoring in the vicinity of a Superfund clean-up site detected 2,3,7,8-TCDD levels on the order of 1 pg/m^3 (0.08 ppq) (Fairless et al. 1987). The surface and subsurface soils at the site were tested and found to contain 2,3,7,8-TCDD at concentrations above 1 ppb at most locations within the site.

2,3,7,8-TCDD has been detected in air samples (concentrations unspecified) collected at 9 of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). CDDs have been detected in air samples (concentrations unspecified) collected at 10 of the 126 NPL sites where they have been detected in some environmental media. TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD

have been detected in air samples (concentrations unspecified) at 10, 3, 3, 3, and 1 sites of the 105, 34, 43, 49, and 53 sites, respectively, where they have been detected in some environmental media (see Table 5-1).

In conclusion, most of the measurements of CDDs in air tend to be very close to current detection limits. CDDs are found at the greatest concentrations in urban air with OCDD being the most prevalent congener (up to 0.100 ppq), HpCDDs being the next most common congener, and 2,3,7,8-TCDD being the least common congener (0.014 ppq). Concentrations of all CDDs are highest in the air near industrial areas. Rural areas usually have very low or unquantifiable levels of all CDDs. In urban and suburban areas, concentrations of CDDs may be greater during colder months of the year when furnaces and wood stoves are used for home heating.

5.4.2 Water

Precipitation samples collected in a rural location (Dorset, Ontario) over an 8-month period between 1986 and 1987 were analyzed for CDDs (Tashiro et al. 1989a, 1989b). No TCDDs were found in any samples at detection limits of 4–30 ppq. OCDD concentrations were found in 3 samples in the 60–1,200 ppq range. Lower concentrations of HpCDD (70 ppq) were also found (Tashiro et al. 1989a). Precipitation samples were also collected in 1987–88 in urban and rural locations in Canada (Tashiro et al. 1989b). Varying levels of OCDD were detected throughout the sampling period, mainly at the rural location. OCDD was the only CDD detected at the rural site. OCDD concentrations ranged from 35 to 230 ppq, with the median value being slightly below 100 ppq. No seasonal pattern of OCDD concentrations was observed. OCDD was detected in only 2 of the urban precipitation samples at concentrations of 33 and 15 ppq (Tashiro et al. 1989b). Rain collected at Bloomington, IN, between June 1987 and July 1988 showed low concentrations of total CDDs, although OCDD was the most prominent congener in all samples at concentrations ranging from below the detection limit of 0.1 pg/L to 220 pg/L. Total TCDD was detected in only 3 of 28 samples at concentrations <9 pg/L (EPA 1991d).

An analysis of EPA's STORET (STOrage and RETrieval) database for 1980–82 showed that based on the statistical criteria used, 2,3,7,8-TCDD was detected but at concentrations too low to be quantified in surface-water samples collected at sampling sites (Staples et al. 1985). The sampling sites in the STORET database included both ambient and pipe sites. Ambient sites included streams, lakes, ponds, wells, reservoirs, canals, estuaries, and oceans and were intended to be indicative of general U.S. waterway conditions. Pipe sites referred to municipal or industrial influents or effluents (Staples et al. 1985).

Treated effluents from various Ontario pulp and paper plants using either the bleached kraft (8 mills) or sulfite bleaching process (2 mills) were analyzed for CDDs (Clement et al. 1989). 2,3,7,8-TCDD was not detected in any of the effluent samples with detection limits ranging from 0.07 to 0.7 ppt. A few samples contained a TCDD isomer (not 2,3,7,8-TCDD) at concentrations ranging from 0.06 to 0.12 ppt. PeCDD (0.07 ppt) was detected in one effluent sample, and OCDD (0.05–0.79 ppt) was detected in 4 effluent samples. Suspended particulates were collected from the final effluent from two plants. 2,3,7,8-TCDD and OCDD were detected in the particulates at a concentration range of 200–660 ppt and 180–210 ppt, respectively. The concentration of 2,3,7,8-TCDD determined in the particulates represents levels in the final effluent of 5–10 ppq, suggesting that 2,3,7,8-TCDD is associated with suspended particulate materials in the effluents (Clement et al. 1989).

In 1983, Jobb et al. (1990) conducted a survey of 49 drinking water supplies in Ontario, Canada, including supplies in the vicinity of chemical plants and pulp and paper mills. OCDD was detected in 36 of 37 positive samples ranging from concentrations of 9 to 175 ppq in raw samples (33 positive samples) and from 19 to 46 ppq in treated (filtered) water samples (4 positive samples). These low concentrations were found primarily in water obtained downstream of industrial areas in the St. Clair/Detroit River system. Concentrations of 2,3,7,8-TCDD were not detected in any sample. Because CDDs are hydrophobic, concentrations of these compounds in water tend to be adsorbed onto particulate matter in water. Conventional water treatment processes are expected to be effective in removing the CDDs along with the particulates. This is substantiated by the fact that only 4 of the 37 positive detections were found in treated drinking water, while 33 detections were found in raw water samples.

During 1986, a survey of 20 community water systems throughout the state of New York was conducted to evaluate CDD/CDF concentrations (Meyer et al. 1989). The sampling sites selected were representative of major surface water sources in the state used to obtain drinking water. The sites included surface water sources receiving industrial discharges and those known to contain CDD-contaminated fish, as well as water sources from more remote areas. Raw water sampled at the Lockport, NY, facility contained concentrations of TCDDs (1.7 ppq) as well as concentrations of TCDFs to OCDFs (18, 27, 85, 210, and 230 ppq, respectively). These data show that the CDF congener group concentrations increased with increasing chlorine numbers. TCDFs were also detected in finished water sampled at the Lockport facility (duplicate samples contained 2.1 and 2.6 ppq). Except for a trace of OCDF detected at one other location, no other CDDs/CDFs were detected in finished water at any of the other 19 community water systems surveyed.

Utility telecommunication and railway right-of-ways may be contaminated by leaching of CDDs associated with chlorophenol-treated railway ties and utility poles. A study in British Columbia showed that CDDs and CDFs were not detected in parkland ditch water (control area), but were detected in farmland, utility, and railway right-of-way ditch water (Wan and van Oostdam 1995). Total mean CDD concentrations (mainly OCDD and HpCDD) measured in farm ditch water, and railway ditch water, without and with utility poles were 2.22 µg/L, 45 µg/L, and 9,627 µg/L respectively. Mean total concentrations of CDDs were much higher in ditch water adjacent to utility poles (13,142 ng/L) than in ditch water 4 meters downstream (4,880 ng/L) or 4 meters upstream of the utility poles (2.72 ng/L). The authors concluded that utility poles and railway ties are a potential constant source of CDD/CDF contamination to both water and sediment in aquatic environment through ditch runoff.

2,3,7,8-TCDD has been detected in surface water samples collected at 9 sites of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). CDDs have been detected in surface water samples collected at 14 of the 126 NPL sites where they have been detected in some environmental media. TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD have been detected in surface water samples at 10, 1, 4, 4, and 6 sites of the 105, 34, 43, 49, and 53 NPL sites, respectively, where they have been detected in some environmental media (see Table 5-1).

Groundwater in the vicinity of an abandoned wood treatment facility was sampled from monitoring wells constructed at depths ranging from 6.1 to 30.5 meters and was analyzed for CDDs in January 1984 (Pereira et al. 1985). Concentrations of HxCDD, HpCDD, and OCDD in groundwater samples taken from wells at a depth of 6.1 meters were 61 ppt, 1,500 ppt, and 3,900 ppt, respectively. The authors noted that the high concentrations of CDDs in the sample from a depth of 6.1 meters probably resulted from the presence of microemulsions of oil that were difficult to separate from the sample. Groundwater samples collected from deeper wells (12.2–30.5 meters) contained HxCDD, HpCDD, and OCDD at concentration ranges of not detected to 21 ppt, not detected to 34 ppt, and not detected to 539 ppt, respectively (Pereira et al. 1985).

2,3,7,8-TCDD has been detected in groundwater samples collected at 15 sites of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). CDDs have been detected in groundwater samples collected at 32 of the 126 NPL sites where they have been detected in some environmental media. TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD have been detected in

groundwater samples at 21, 3, 10, 14, and 16 sites of the 105, 34, 43, 49, and 53 NPL sites, respectively, where they have been detected in some environmental media (see Table 5-1).

In conclusion, CDDs are rarely detected in drinking water at ppq levels or higher. Raw water samples generally have higher concentrations of CDDs (9–175 ppq) than finished drinking water samples (19–46 ppq) because conventional water treatment processes remove the CDDs along with the particulates from raw water. CDDs have been detected in treated effluent samples collected at pulp and paper mills using the bleach kraft or sulfite bleaching process. In groundwater samples collected near industrial sites, CDDs have been detected at concentrations up to 3,900 ppt.

5.4.3 Sediment and Soil

Soil. As part of this National Dioxin Study, EPA conducted a 2-year nationwide study to assess the extent of 2,3,7,8-TCDD contamination (EPA 1987n). Environmental samples (including soil, sediment, water, and fish) were analyzed for 2,3,7,8-TCDD concentrations at seven different tiers of sites (including NPL, various industrial, urban, and pristine rural sites). Soil concentrations at most of the Tier 1 and 2 sites (i.e., sites classified as or expected to be classified as NPL sites) were in the ppb range, although at a few of the sites where 2,4,5-TCP production waste storage or disposal occurred, concentrations were as high as 2,000 ppm. Offsite soil contamination of concern (in the ppb range) was confirmed at 7 of these 100 Tier 1 and 2 sites. At 11 of 64 Tier 3 sites (facilities and associated disposal sites where 2,4,5-TCP and its derivatives were formulated into pesticide products), soil concentrations exceeded 1 ppb, but in 7 of the 11 sites where contamination was found, only 1 or 2 samples exceeded 1 ppb. At 15 of 26 Tier 5 sites (areas where 2,4,5-TCP and other pesticide derivatives had been or were currently being used), soil concentrations were generally above 1 ppt with one detection at 6 ppb. Two-thirds of all detections at the Tier 5 sites were below 5 ppt. At 3 of 18 Tier 6 sites (organic chemical and pesticide manufacturing facilities where production processes could have resulted in 2,3,7,8-TCDD being introduced into the waste streams), soil concentrations exceeded the 1 ppt detection limit, although these concentrations were limited to one or two samples per site. In general, 2,3,7,8-TCDD was detected infrequently and at very low concentrations in background soil samples taken at sites (urban and rural areas) that did not have previously known sources of 2,3,7,8-TCDD contamination (1 ppt detection limit). Only 17 of 221 urban sites and 1 of 138 rural sites in Tier 7 (background sites not expected to have contamination) had detectable levels of 2,3,7,8-TCDD, with 11.2 ppt being the highest concentration reported (Des Rosiers 1987; EPA 1987n).

Background levels of CDDs in soil were measured at Elk River, Minnesota, a semi-rural area located about 25 miles northwest of Minneapolis-St. Paul (Reed et al. 1990). No major industrial or commercial activity occurred in the area at the time of the study. The soil data reflected generally low background concentrations of CDDs. 2,3,7,8-TCDD, total TCDD, and PeCDD were not detected (detection limit range 0.75–2.9 ppt). OCDD represented the highest baseline levels, ranging from 340 to 3,300 ppt. Levels of total HpCDD ranged from 62 to 640 ppt, while levels of total HxCDD ranged from 12 to 99 ppt (Reed et al. 1990).

Birmingham (1990) analyzed soil samples from industrial, urban, and rural sites in Ontario, Canada, and some Midwestern U.S. states for CDDs and CDFs. The concentrations of CDD/CDF in rural soils were generally not detectable, although HpCDDs and OCDD were found in a few samples. In urban soils, the tetra- through octa-congener groups were measured for both CDDs and CDFs. The HpCDDs and OCDD dominated the homologue profile and were two orders of magnitude greater than concentrations in rural soils. These urban soils also contained measurable quantities of TCDDs, PeCDDs, and HxCDDs. Industrial soils did not contain any TCDDs or PeCDDs, but they did contain the highest concentrations of the HpCDDs, OCDD, TCDFs, HpCDFs, and OCDFs. In an earlier study, soil concentrations of 2,3,7,8-TCDD were measured in industrialized areas of a group of mid-western and mid-Atlantic states (Illinois, Michigan, New York, Ohio, Pennsylvania, Tennessee, Virginia, and West Virginia) (see Table 5-4) (Nestrick et al. 1986). Many of the samples were taken within one mile of major steel, automotive, or chemical manufacturing facilities or of municipal solid-waste incinerators. The data show that in these typical industrialized areas, 2,3,7,8-TCDD soil concentrations are below 0.01 ppb (range, ND–9.4 ppt). The widespread occurrence of 2,3,7,8-TCDD in U.S. urban soils at levels of 0.001–0.01 ppb suggests that local combustion sources, including industrial and municipal waste incinerators, are the probable sources of the trace 2,3,7,8-TCDD soil concentrations found in those locations (Nestrick et al. 1986). Soil samples collected in the vicinity of a sewage sludge incinerator were compared with soil samples from rural and urban sites in Ontario, Canada (Pearson et al. 1990). Soil in the vicinity of the incinerator showed a general increase in CDD concentration with increasing degrees of chlorination. Of the CDFs measured, only OCDFs was detected (mean concentration, 43 ppt). Rural woodlot soil samples contained only OCDD (mean concentration, 30 ppt). Soil samples from undisturbed urban parkland revealed only concentrations of HpCDDs and OCDD, but all CDF congener groups from TCDF to OCDF were present. The parkland samples showed an increase in concentrations from the HpCDDs to OCDD and PeCDFs to OCDF. The TCDFs were found at the highest concentration (mean, 29 ppt) of all the CDF congener groups.

Table 5-4. 2,3,7,8-TCDD Levels Measured in Soil Samples Collected in 1984 from Industrialized Areas of U.S. Cities

Sample location[a]	2,3,7,8-TCDD (ppq)
Lansing, MI	3,000 (700)[b] ND (800)
Gaylord, MI	ND (200)
Detroit, MI	3,600 (700) 2,100 (400)
Chicago, IL	9400 4200
Middletown, OH	ND (300) ND (300)
Barberton, OH	5600
Akron, OH	6300
Nashville, TN	800 (300)
Pittsburgh, PA	2,600 (500)
Marcus Hook, PA	400 (300)
Philadelphia, PA	900 (300)
Clifton Heights, PA	ND (400)
Brooklyn, NY	2,600 (400)
South Carolina, WV	ND (400)
Arlington, VA	ND (400)
Newport News, VA	400 (300)

[a] Post office state abbreviations used
[b] Values in parentheses show the detection limit, 2.5 times noise, when the experimental result is less than 10 times the measured detection limit.

ND = not detected; ppq = parts per quadrillion; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Source: Nestrick et al. 1986

A large-scale environmental survey was conducted by the Dow Chemical Company to determine soil levels of 2,3,7,8-TCDD on the Dow Midland Plant site and in the city of Midland, Michigan (Nestrick et al. 1986). The Dow Midland Plant site manufactures a variety of chlorophenolic compounds. Soil samples were taken from three different types of areas: locations known to be directly associated with current or historic chlorophenolic production and handling, locations known to be associated with incineration of chemical and conventional wastes and with ash storage, and locations away from established 2,3,7,8-TCDD sources that provide a measure of general background levels of 2,3,7,8-TCDD surface soil within the Dow property. Soil samples taken from chlorophenolic production areas showed a range of 2,3,7,8-TCDD concentrations from 0.041 to 52 ppb. Two localized areas of elevated concentrations (above 5 ppb) were identified with peaks at 34 ppb and 52 ppb. All other samples taken around this area had 2,3,7,8-TCDD soil concentrations below 1 ppb. Two of 10 surface soil samples with 2,3,7,8-TCDD concentrations above 1 ppb (2.0 and 4.3 ppb) were found near the waste incinerator. The concentrations observed there (0.018–4.3 ppb) closely matched the 2,3,7,8-TCDD content of the ash produced by the incinerator, which ranged up to 10 ppb. The background levels of 2,3,7,8-TCDD (0.0065–0.59 ppb) within the Dow Midland Plant site were well below 1 ppb. Soil samples taken within the city of Midland showed 2,3,7,8-TCDD soil concentrations below the 1 ppb concern level established by the U.S. Public Health Service, Centers for Disease Control and Prevention (CDC), for residential areas (Kimbrough et al. 1984). 2,3,7,8-TCDD soil concentrations in the city of Midland (0.6–450 ppt) were higher in areas nearer the Dow Chemical Company Midland Plant site (22–450 ppt) (Nestrick et al. 1986). This gradient suggests that operations on the Midland Plant site are associated with the appearance of the trace levels of 2,3,7,8-TCDD in the nearby environment.

Several studies have analyzed soil samples in the State of Missouri for 2,3,7,8-TCDD contamination and all reported values are comparable. Concentrations of 2,3,7,8-TCDD in soil samples from contaminated sites throughout Missouri ranged from 30 to 1,750 ppb and concentrations in Times Beach, MO, a heavily contaminated site ranged from 4.4 to 317 ppb (Tiernan et al. 1985). In another study, soil core samples taken from a roadside in Times Beach, MO, contained levels of 2,3,7,8-TCDD ranging from 0.8 to 274 ppb. Many roadways in Times Beach had been sprayed with waste oil containing CDDs for dust control (Freeman et al. 1986). In a third study conducted by Hoffman et al. (1986), 2,3,7,8-TCDD was measured in soil samples from the Quail Run Mobile Home Park in Gray Summit, MO. A maximum soil concentration of 2,200 ppb (single non-composited sample) was detected at one site; however, concentrations typically ranged from 39 to 1,100 ppb in composite soil samples.

2,3,7,8-TCDD has been detected in soil samples collected at 61 sites of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). CDDs have been detected in soil samples collected at 94 of the 126 NPL sites where they have been detected in some environmental media. TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD have been detected in soil samples at 71, 21, 29, 34, and 38 sites of the 105, 34, 43, 49, and 53 NPL sites, respectively, where they have been detected in some environmental media (see Table 5-1).

In conclusion, soil concentrations of CDDs are typically higher in urban areas than in rural areas. Soil concentrations associated with industrial sites are clearly the highest, with CDD levels ranging from the hundreds to thousands of ppt. In general, as the degree of chlorination increases, the concentrations increase. HpCDD and OCDD congeners are generally found at higher concentrations in soil and sediments than the TCDD, PeCDD, and HxCDD congeners.

Sediment. Highly stratified sediments from Green Lake in upstate New York had CDD concentrations that could be correlated with atmospheric deposition. CDDs could be detected as far back as 1860–1865 at a total CDD concentration of 7 ppt; 98% of all CDDs detected were OCDD. The CDD sediment profile showed a strong increase after 1923 and continued to increase until 1984 (the last year analyzed), with a maximum concentration of >900 ppt, of which 75% was OCDD (Smith et al. 1992).

In another study, surficial (surface) sediment samples taken from the Saginaw River and Bay and from southern Lake Huron showed that CDDs are ubiquitous in the samples studied, including the most remote locations (Czuczwa and Hites 1984). The concentrations were highest in those sediments collected closest to urban areas and lowest in open-lake cores. This indicates that the most of the CDDs found in these samples are anthropogenic in origin (Czuczwa and Hites 1984). The CDDs found closest to urban areas may be related to point source industrial inputs as well as atmospheric deposition, while CDDs found at the remote sites are likely to be only atmospheric in origin. In dated sediment cores, CDDs were absent before 1940. Thus, the authors suggest that accumulation of CDDs in the environment is a recent phenomenon and is related to industrial activities (Czuczwa and Hites 1986a, 1986b). Surface sediments taken from the Great Lakes showed that CDDs were ubiquitous in the sediments. OCDD was predominant at concentrations ranging from 560 to 4,800 ppt (dry weight) (Czuczwa and Hites 1986a, 1986b). The sediments also contained relatively high concentrations of HpCDD. The less chlorinated CDDs were not found in the sediments (Czuczwa and Hites 1986a). Sediment samples were collected from five sampling stations in the western basin of Lake Ontario near the mouth of the Niagara River and were analyzed for 2,3,7,8-TCDD

(Onuska et al. 1983). Measurable quantities of 2,3,7,8-TCDD were present in sediment at two of the stations. The highest concentration of 2,3,7,8-TCDD (13 ppt) was found at a depth of 3–5 cm, followed by a concentration of 4 ppt at a depth of 3 cm, and 3 ppt at a depth of 13–14 cm. Concentrations of 2,3,7,8-TCDD in the rest of the sediment samples were below the detection limit (0.1 ppt) (Onuska et al. 1983).

Surficial sediments collected from Jackfish Bay on the north shore of Lake Superior, near a pulp and paper manufacturer, contained moderate concentrations of the TCDFs (range of geometric mean, 2.4–6,223 pg/g) and OCDD congeners (range of geometric mean, 12–250 pg/g), with trace (< 60 ppt) concentrations of other congeners (Sherman et al. 1990). The OCDF and OCDD profile for a sediment core collected from Moberly Bay was similar to the surficial sediment pattern. These congener groups predominated at all sediment depths where detectable concentrations occurred. Low concentrations of the HpCDD, PeCDF, and HpCDF congeners also were detected. The concentration profile of the HpCDF congener group showed a relatively high value that dropped abruptly to nondetectable (<60 ppt) below a sediment depth of 10 cm. This abrupt change corresponded to a date of 1973 that reflected an operational change at the pulp mill.

Surficial harbor sediments collected near a PCP wood preserving plant in Thunder Bay, Ontario, Canada on the north shore of Lake Superior were found to contain CDDs and CDFs (McKee et al. 1990). The highest concentrations were detected at stations closest to the plant docking area and lower concentrations occurred at stations further from the source (McKee et al. 1990). No CDDs or CDFs were detected below the surficial layer. Concentrations of TCDD and PeCDD congeners were below detection limits (<1 ppt) in all samples. The concentrations of the HxCDD and OCDD congeners increased with the degree of chlorination. The maximum concentrations of the HxCDDs to OCDD ranged from 5,600 ppt (HxCDDs) to 980,000 ppt (OCDD). As with the CDD distribution profile, the concentrations of HxCDFs and OCDFs increased with the degree of chlorination.

Sediment samples taken from Love Canal storm sewers in Niagara Falls, NY, contained from 0.9 to 312 ng/g of 2,3,7,8-TCDD (0.9–312 ppb) (Smith et al. 1983). The highest concentration of 2,3,7,8-TCDD (312 ppb) was found immediately adjacent to the canal at its southern end; the next highest concentration (120 ppb) was found just upstream. A sample taken one street away from the canal, near the high altitude division of the storm sewer system where only a small amount of canal runoff occurs, contained only 0.9 ppb 2,3,7,8-TCDD (Smith et al. 1983).

Surface sediment samples were collected from various estuaries in the United States: Black Rock Harbor (an urban industrialized estuary in Connecticut), Long Island Sound (a relatively clean reference site in New York), Narragansett Bay (an estuary affected by input from chemical industries in Rhode Island), New Bedford Harbor (an estuary within a Superfund site boundary in Massachusetts), and Eagle Harbor (a creosote wood-treatment facility in Washington) (Norwood et al. 1989). 2,3,7,8-TCDD was detected in sediment from Black Rock Harbor (56–57 ppt), Narragansett Bay (15–19 ppt), and in some of the sediment samples found in New Bedford Harbor (4.2–4.6 ppt). 1,2,3,7,8-PeCDD was detected in estuarine sediments from Black Rock Harbor (79–95 ppt), New Bedford Harbor (21–29 ppt), and Eagle Harbor (5 ppt). HxCDD, HpCDD, and OCDD were also detected in sediments from all estuaries at concentrations ranging from approximately 10–100 ppt, 500–3,000 ppt and 2,000–37,000 ppt, respectively. The highest concentrations of HpCDD (>1,000 ppt) were detected in Narragansett Bay sediments, while the highest concentration of OCDD (37,000 ppt) was detected in Eagle Harbor sediments. The levels of CDDs reported for all samples were for dry weight (air dried) concentrations (Norwood et al. 1989).

Sediment samples collected in 1985–86 from estuarine areas (Passaic River and Newark Bay), near a Newark, NJ, facility that manufactured 2,4,5-T between 1948 and 1969, contained high concentrations of 2,3,7,8-TCDD and OCDD (Bopp et al. 1991). Concentrations of OCDD in the sediment were many times higher than concentrations of 2,3,7,8-TCDD. The study indicated that there probably was a significant regional source (i.e., combustion and/or use of the wood preservative PCP) for OCDD, a source that is lacking in significant concentrations of 2,3,7,8-TCDD relative to the local industrial source. A high correlation was found between 2,3,7,8-TCDD and 2,3,7,8-TCDF concentrations, suggesting that the industrial site was a major source of 2,3,7,8-TCDF to the natural waters of the area. Sediment core samples from a depth of 108–111 cm contained 2,3,7,8-TCDD at a concentration of 21,000 ppt, the highest concentration measured in the study. This residue value corresponds to deposition of sediments that occurred during the late 1950s to early 1960s during active 2,4,5-T production at the industrial site. Maximum concentrations of TCDD in the sediment cores corresponded to the period of maximum 2,4,5-T production, with more recently deposited sediments containing lower concentrations of TCDD. This study established the persistence of 2,3,7,8-TCDD and 2,3,7,8-TCDF in anaerobic sediments on a time scale of several decades (Bopp et al. 1991).

There has been considerable discussion about historic releases of CDDs/CDFs in Newark Bay, New Jersey. Bopp et al. (1991) suggested that a single source (pesticide production facility) is responsible for the presence of 2,3,7,8-TCDD/TCDF in the watershed. Recently, Wenning et al. (1992, 1993a, 1993b),

using chemometric comparisons of CDD/CDF residues in surficial sediments, found that congener patterns in Newark Bay were closely related to those found in sediments from other industrialized waterways with several different pollutant sources (e.g., New Bedford Harbor, Massachusetts; Black Rock Harbor, Connecticut; Providence River, Rhode Island; Eagle Harbor, Washington, as well as several European waterways). The similarities and differences among the various waterways examined in the analysis suggests that the presence of 2,3,7,8-substituted CDDs/CDFs in surficial sediments from Newark Bay are more likely due to multiple sources of contamination. Most recently, Ehrlich et al. (1994) identified the relative contributions of various sources of CDDs/CDFs to recently deposited sediments of Newark Bay using polytopic vector analysis, a multivariate statistical technique. These authors also concluded that the 2,3,7,8-substituted CDD/CDF patterns in the sediments of Newark Bay are consistent with discharges from multiple sources. In a recent study, Huntley et al. (1997) reported that combined sewer overflows may contribute substantially to surface sediment contamination of the nearby Passaic River. Several such sources that have existed over the past century in the vicinity include scrap metal refineries, pulp and paper mills, copper smelters, chemical manufacturing plants, municipal sewage treatment plants, and industrial/ municipal incinerators (EPA 1987n). 2,3,7,8-TCDD sediment concentrations ranged from below the detection limit (22 ppt) to 21,000 ppt (21 ppb), whereas OCDD concentrations ranged from 3.1 ppb to 42,000 ppt (42 ppb), although other sources of OCDD were thought to contribute to the elevated levels of OCDD (Bopp et al. 1991; Wenning et al. 1992).

Sludges from various Ontario pulp and paper plants using either the bleached kraft (8 mills) or sulfite bleaching process (2 mills) were analyzed for CDDs (Clement et al. 1989). 2,3,7,8-TCDD was detected in sludge samples at a concentration range of 170–370 ppt. Only one other TCDD isomer (180 ppt) was detected in a sludge sample, but it was not identified. PeCDDs and HxCDDs were not detected in any sludge samples, whereas HpCDD (400 ppt) was found in 1 sludge sample and OCDD (120–1,800 ppt) was found in 6 sludge samples (Clement et al. 1989).

Utility telecommunication and railway right-of-ways may be contaminated by leaching of CDDs associated with chlorophenol-treated railway ties and utility poles. A study in British Columbia showed that CDDs and CDFs were not detected in parkland ditch sediments (control area), but were detected in farmland, utility, and railway right-of-way ditch sediments (Wan and van Oostdam 1995). Total mean CDD concentrations (mainly OCDD and HpCDD) ranged from 18.8 to 277 ng/kg (ppt) (dry weight) in ditch sediments and ballasts respectively. Concentrations of CDDs were much higher in ditch sediment adjacent to utility poles (mean 2,576 ng/kg (ppt) [dry weight]) than in sediment 4 meters downstream (14 ng/kg

[dry weight]) or 4 meters upstream of the utility poles (not detected). CDD concentrations in ditch water were also higher close to the poles (mean 13,142 ng/L [ppt] than 4 meters downstream of the poles (mean 4,880 ng/L [ppt]). The authors concluded that utility poles and railway ties are a potential constant source of CDD/CDF contamination to both water and sediment in aquatic environment through ditch runoff.

2,3,7,8-TCDD has been detected in sediment samples collected at 17 sites of the 91 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). CDDs have been detected in sediment samples collected at 31 of the 126 NPL sites where they have been detected in some environmental media. TCDDs, PeCDDs, HxCDDs, HpCDDs, and OCDD have been detected in sediment samples at 22, 7, 10, 9, and 13 sites of the 105, 34, 43, 49, and 53 NPL sites, respectively, where they have been detected in some environmental media (see Table 5-1).

In conclusion, CDD congener profiles in sediment generally reflect those exhibited by the contamination source or sources. High concentrations of HxCDDs, HpCDDs, and OCDDs in sediment are usually the result of anthropogenic inputs via industrial processes and releases or urban runoff, and concentrations generally increase with the degree of chlorination, but decrease with distance from the source (McKee et al. 1990).

5.4.4 Other Environmental Media

Foods. The FDA has conducted limited analyses for the higher chlorinated CDDs (HxCDD, HpCDD, and OCDD) in market-basket samples collected from 1979 to 1984 under the FDA's Total Diet Program (Firestone et al. 1986). Food samples found to contain PCP residues >0.05 µg/g (ppm) were analyzed for 1,2,3,4,6,7,8-HpCDD and OCDD. In addition, selected samples of ground beef, chicken, pork, and eggs from the market-basket survey were analyzed for these CDD congeners (wet weight basis), regardless of the results of the PCP analysis. HxCDD was not found in any of the foods sampled; however, the detection limit (10–40 pg/g [ppt]) was very high. Generally low concentrations (<300 pg/g [ppt]) of HpCDD and OCDD were found in bacon, chicken, pork chops, and beef liver. Several beef livers had higher concentrations of OCDD residues (614–3,830 pg/g), and one beef liver contained 428 pg/g (ppt) of HpCDD. HxCDD, HpCDD, and OCDD were not detected in milk, ground beef, or seafood samples, but the detection limits (10–40 ppt) were very high. No CDDs were found in 17 egg samples collected in various parts of the United States. OCDD was detected in 2 of 18 pork samples (27 ppt and 53 ppt) and in 2 of the 16 chicken samples (29 ppt and 76 ppt). One chicken sample with PCP residues (>0.05 µg/g) contained

concentrations of 1,2,3,4,6,7,8-HpCDD (28 ppt) and OCDD (252 ppt). The CDD residues (21–1,610 pg/g) in eggs from Houston, Texas, and Mena, Arkansas, with PCP residues >0.05 µg/g collected in 1982 and 1983–84, respectively, contained 1,2,3,4,6,7,8-HpCDD concentrations ranging from 21 to 588 ppt, and OCDD concentrations ranging from 80 to 1,610 ppt. These residues were attributed to local PCP contamination problems in these areas (Firestone et al. 1986). Milk samples contaminated with PCP at levels ranging from 0.01 µg/g to 0.05 µg/g PCP contained no detectable CDDs. It should be noted that the reported limits of detection (10–40 ppt) for the FDA analyses from these older samples, are higher than concentrations of CDDs observed in foods from more recent studies. Samples of beef liver, pork chops, chicken, ground beef, and eggs collected in the United States and analyzed for HpCDD and OCDD contained average concentrations of HpCDD (2.2–9.6 ppt) and OCDD (6.3–47.6 ppt) (Jasinski 1989). Eggs contained the lowest levels of HpCDD and OCDD, and beef liver contained the highest levels.

LaFleur et al. (1990) analyzed the concentration of 2,3,7,8-TCDD and 2,3,7,8-TCDF (wet weight basis) in a variety of food products collected randomly from grocery stores located in the southern, Midwestern, and northwestern regions of the United States. Concentrations of 2,3,7,8-TCDD ranged from 17 to 62 pg/kg for ground beef, were not detectable in ground pork, ranged from 12 to 37 pg/kg for beef hot dogs, and ranged from 7.2 to 9.4 pg/kg for canned corned beef hash on a whole-weight basis. Concentrations of 2,3,7,8-TCDF were generally much less than concentrations of 2,3,7,8-TCDD, with the exception of ground pork and corned beef hash. For ground pork, TCDD concentrations were not detectable and 2,3,7,8-TCDF concentrations ranged from 13 to 20 pg/kg and for corned beef hash, concentrations of TCDD ranged from 7.2 to 9.4 pg/kg, while concentrations of TCDF ranged from 9.8 to 10 pg/kg.

A study conducted by the province of Ontario, Canada analyzed concentrations of CDDs/CDFs in a variety of foods locally grown in Canada or imported from the United States and New Zealand (Birmingham et al. 1989). Concentrations of OCDD in various foods ranged from 3 to 210 ppt (wet weight basis). OCDD concentrations were detected in U.S. eggs (8 ppt), U.S. beef (24 ppt), Canadian hamburger (3 ppt), and Canadian chicken samples (210 ppt). Chicken also contained 15 ppt HpCDD, but no other CDDs were detected in these samples. Fruits and vegetables were generally free of CDD and CDF residues (detection limit = 1 ppt). OCDD concentrations ranging from 0.6 to 8 ppt (wet weight) were also detected in samples of U.S. potatoes (3 ppt), apples (8 ppt), peaches (0.6 ppt), and wheat (0.7 ppt). For these food items, OCDD was the only homologue detected. No 2,3,7,8-TCDD was detected in any of the food samples tested (detection limits of 1–4 ppt).

Beck et al. (1989a) analyzed the concentrations of CDDs/CDFs in 22 samples of foodstuffs collected in the Federal Republic of Germany. Twelve randomly collected food samples (chicken, eggs, butter, pork, redfish (ocean perch), cod, herring, vegetable oil, cauliflower, lettuce, cherries, and apples) were purchased in various stores in West Berlin. The highest 2,3,7,8-TCDD levels were observed in fish samples with concentrations of 4.7, 23, and 2.8 ppt (lipid basis) for herring, cod, and redfish, respectively. Concentrations of 2,3,7,8-TCDD (on a lipid basis) in meat, poultry, and dairy products were lower; with concentrations ranging from 0.01 ppt in sheep, 0.03 in pork, 0.2 in eggs, 0.3 in chicken, 0.6 in cattle, and 0.02 in cow's milk and 0.08 in butter (see Table 5-5). The EPA TEQ values for CDDs/CDFs calculated for these products ranged from 20.0–39.7 ppt in fish, 0.14–1.31 ppt in meat and poultry, and from 0.43 to 0.86 ppt in dairy products. In all samples tested, the 2,3,7,8-substituted congeners predominated in the samples and non-2,3,7,8-substituted congeners were not detected in fish, chicken and eggs. For meat, poultry, and dairy samples, the congener profile showed high concentrations of 1,2,3,4,6,7,8-HpCDD and OCDD with concentrations of most other congeners at or below 1 ppt (lipid basis). In fish samples, high concentrations of the 2,3,7,8-substituted congeners, TCDDs (range 2.8–23 ppt), PeCDD (range 1.3–12 ppt), HxCDD (range 0.01–17 ppt), and OCDD (range 11–83 ppt) resulted in TEQ values for CDDs/CDFs ranging from 20–40 ppt (lipid basis). In the five food samples of plant origin, no CDDs/CDFs were detected on a whole weight basis (detection limit . 0.01 ppt).

Congener-specific analyses for CDDs and CDFs were performed on 18 dairy, meat, and fish products obtained from a supermarket in upstate New York (Schecter et al. 1994d). Total CDD concentrations (on a wet weight basis) ranged from 0.35 to 2.91 ppt in fish, 0.6–59.3 ppt for meats, and 0.6–14 ppt in dairy products. A summary of the CDD/CDF concentrations and TEQ concentrations calculated for the 18 foods is presented in Table 5-6. The TEQ for both the CDDs and CDFs on a wet weight basis for these food samples ranged from 0.02 to 1.5 ppt, 0.02–0.13 ppt for fish products, 0.03–1.5 ppt for meat products, and 0.04–0.7 ppt for dairy products, with the highest TEQ found in ground beef.

Recently, the EPA and U.S. Department of Agriculture (USDA) completed the first statistically designed surveys of the occurrence and concentrations of CDDs/CDFs in beef fat (Ferrario et al. 1996; Winters et al. 1996), pork fat (Lorber et al. 1997), poultry fat (Ferrario et al. 1997), and the U.S. milk supply (Lorber et al. 1998). The congener specific results for various foods are shown in Table 5-7. It is clear from the results, that two congeners (1,2,3,4,6,7,8-HpCDD and 1,2,3,4,6,7,8-OCDD) were typically found at the highest concentrations in all food samples. Concentrations of 2,3,7,8-TCDD were highest in heavy fowl (0.43 ppt) and young turkeys (0.24 ppt); much lower concentrations were found in beef (0.05 ppt), pork

Table 5-5. CDD/CDF Concentrations in Food Samples of Animal Origin (ppt, lipid basis)

	Dairy products		Meat					Fish		
Congener	Cow's milk	Butter	Pork	Cattle	Sheep	Chicken	Eggs	Herring	Cod	Redfish
2,3,7,8-TCDF	0.7	0.15	0.11	0.3	0.6	2.1	1.1	57.0	98.0	78.0
2,3,7,8-TCDD	0.2	0.08	0.03	0.6	0.01	0.3	0.2	4.7	23.0	2.8
1,2,3,7,8-PeCDF	0.2	0.09	0.01	0.01	0.01	0.01	0.6	16.0	48.0	31.0
2,3,4,7,8-PeCDF	1.4	0.45	0.08	1.5	0.9	1.5	0.8	29.0	3.1	25.0
1,2,3,7,8-PeCDD	0.7	0.41	0.12	0.8	0.5	0.7	0.4	12.0	1.3	6.5
1,2,3,4,7,8-HxCDF	0.9	0.43	0.15	0.8	0.9	0.6	0.4	3.0	6.9	3.5
1,2,3,6,7,8-HxCDF	0.8	0.44	0.07	0.6	1.2	0.4	0.3	4.2	13.0	6.0
2,3,4,6,7,8-HxCDF	0.7	0.31	0.05	1.3	1.5	0.3	1.7	3.6	8.2	7.2
1,2,3,4,7,8-HxCDD	0.3	0.15	0.21	0.6	0.3	0.5	1.3	1.2	0.01	0.5
1,2,3,6,7,8-HxCDD	1.1	0.95	0.29	1.9	1.5	2.8	1.4	5.8	17.0	8.4
1,2,3,7,8,9-HxCDD	0.4	0.26	0.06	0.6	0.4	0.6	5.0	1.0	5.2	1.3
1,2,3,4,6,7,8-HpCDF	0.5	0.34	1.1	2.2	8.1	0.8	0.6	1.6	10.0	1.5
1,2,3,4,6,7,8-HpCDD	2.0	1.5	2.1	18.0	15.0	6.0	0.4	3.6	10.0	3.0
OCDF	1.0	0.25	0.41	0.2	0.3	0.6	0.2	1.4	2.1	0.3
OCDD	10.0	3.4	19.0	25.0	68.0	52.0	12.0	19.0	83.0	11.0
TEQ	0.86	0.43	0.14	1.31	0.52	1.16	0.80	21.3	39.7	20.0

Source: Beck et al. 1989a

TEQ = toxicity equivalency

Table 5-6. Dioxins, Dibenzofurans, and Dioxin Toxicity Equivalencies (TEQs) in U.S. Foods (ppt, wet weight)

	Total CDDs/CDFs		
Food type	CDD	CDF	TEQ
Fish			
Haddock	0.75	0.14	0.03
Haddock fillet	0.35	0.07	0.02
Crunchy haddock	2.91	0.51	0.13
Perch	1.55	1.14	0.02
Cod	0.82	0.09	0.02
Meats			
Ground beef	4.1	7.0	1.5
Beef rib sirloin tip	0.6	0.2	0.04
Beef rib steak	30.7	4.6	0.3
Pork chop	59.3	2.5	0.3
Cook ham	59.3	2.5	0.3
Lamb sirloin	8.95	0.85	0.4
Bologna	3.7	0.4	0.12
Chicken drumstick	0.95	0.14	0.03
Dairy			
Cottage cheese	0.6	0.3	0.04
Soft blue cheese	14.0	5.0	0.7
Heavy cream	5.0	2.0	0.4
Soft cream cheese	4.0	2.0	0.3
American cheese slices	4.0	2.0	0.3

Source: Schecter et al. 1994d

CDDs = chlorinated dibenzo-*p*-dioxins; CDFs = chlorinated dibenzofurans; TEQ = toxicity equivalency

Table 5-7. Overall National Averages of the Concentrations (ppt, or pg/g) of Dioxin and Furan Congeners in Fat of Meat and Milk on a Lipid Basis[a]

CDD/CDF Congener	Beef (n=63)	Pork fat (n=78)	Young chickens (n=39)	Light fowl (n=12)	Heavy fowl (n=12)	Young turkeys (n=15)	Milk (composites) (n=8)
2,3,7,8-TCCD	0.05 (0.03)	0.10 (0.01)	0.16 (0.15)	0.05 (0.03)	0.43 (0.42)	0.24 (0.24)	0.07 (0.07)
1,2,3,7,8-PeCDD	0.35 (0.04)	0.45 (0.01)	0.24 (0.12)	0.15 (0.00)	0.32 (0.22)	0.32 (0.23)	0.32 (0.32)
1,2,3,4,7,8-HxCDD	0.64 (0.18)	0.52 (0.10)	0.18 (0.05)	0.15 (0.00)	0.24 (0.13)	0.16 (0.03)	0.39 (0.39)
1,2,3,6,7,8-HxCDD	1.42 (1.21)	1.10 (0.80)	0.39 (0.33)	0.34 (0.29)	0.71 (0.70)	0.79 (0.77)	1.87 (1.87)
1,2,3,7,8,9-HxCDD	0.53 (0.26)	0.47 (0.04)	0.39 (0.29)	0.15 (0.01)	0.60 (0.51)	0.17 (0.06)	0.55 (0.55)
1,2,3,4,6,7,8-HpCDD	4.48 (4.39)	10.15 (9.93)	1.53 (1.53)	0.93 (0.93)	2.04 (2.02)	0.54 (0.52)	5.03 (5.03)
1,2,3,4,6,7,8,9-OCDD	4.78 (3.26)	52.77 (52.40)	5.31 (5.31)	2.07 (2.07)	7.67 (7.67)	0.75 (0.68)	4.89 (4.89)
2,3,7,8-TCDF	0.03 (0.00)	0.09 (0.004)	0.28 (0.28)	0.25 (0.25)	0.48 (0.47)	0.57 (0.57)	0.08 (0.08)
1,2,3,7,8-PeCDF	0.31 (0.00)	0.45 (0.00)	0.21 (0.08)	0.18 (0.05)	0.14 (0.02)	0.36 (0.25)	0.05 (0.00)
2,3,4,7,8-PeCDF	0.36 (0.06)	0.56 (0.14)	0.25 (0.12)	0.22 (0.11)	0.18 (0.09)	0.53 (0.47)	0.28 (0.28)
1,2,3,4,7,8-HxCDF	0.55 (0.27)	0.98 (0.60)	0.23 (0.10)	0.16 (0.04)	0.17 (0.06)	0.20 (0.13)	0.39 (0.39)
1,2,3,6,7,8-HxCDF	0.40 (0.12)	0.58 (0.58)	0.20 (0.07)	0.15 (0.03)	0.15 (0.01)	0.17 (0.03)	0.25 (0.25)
1,2,3,7,8,9-HxCDF	0.31 (0.00)	0.45 (0.00)	0.15 (0.00)	0.15 (0.00)	0.15 (0.00)	0.15 (0.00)	0.05 (0.00)
2,3,4,6,7,8-HxCDF	0.39 (0.10)	0.57 (0.16)	0.21 (0.08)	0.14 (0.02)	0.15 (0.02)	0.15 (0.03)	0.28 (0.28)
1,2,3,4,6,7,8-HpCDF	1.00 (0.75)	3.56 (3.35)	0.27 (0.20)	0.15 (0.05)	0.20 (0.10)	0.15 (0.02)	0.83 (0.83)
1,2,3,4,7,8,9-HpCDF	0.31 (0.00)	0.57 (0.17)	0.17 (0.04)	0.15 (0.00)	0.15 (0.00)	0.15 (0.00)	0.05 (0.00)
1,2,3,4,6,7,8,9-OCDF	1.88 (0.00)	2.30 (1.85)	0.34 (0.07)	0.29 (0.00)	0.31 (0.04)	0.29 (0.00)	0.05 (0.00)
Total CDD/CDF, pg/g	17.79 (10.67)	75.67 (70.14)	10.51 (8.82)	5.68 (3.88)	14.09 (12.48)	5.69 (4.03)	15.43 (15.23)
CDD/CDF I-TEQ, pg/g	0.89 (0.35)	1.30 (0.46)	0.64 (0.41)	0.40 (0.16)	0.98 (0.80)	0.93 (0.76)	0.82 NR

a Concentrations calculated at non-detects (ND) equal 1/2 the detection limit (results for ND=0 are in parentheses).

Source: Ferrario et al. 1996, 1997; Lorber et al. 1997; Winters et al. 1996

(0.10 ppt), young chickens (0.16 ppt), light fowl (0.03 ppt) and milk (0.07 ppt). The total concentrations of CDDs/CDFs were highest in pork fat (75.67 ppt) and milk (15.43 ppt), and ranged from 5.68 to 14.09 ppt for all other types of foods tested. The TEQ value for CDDs/CDFs combined was highest for pork fat (1.30 ppt), heavy fowl (0.98 ppt), young turkeys (0.93 ppt), and beef fat (0.89 ppt), with lower TEQ values of 0.40–0.82 ppt for young chickens, light fowl, and milk.

CDDs have been found in infant formulas purchased in the United States (Schecter et al. 1989c). The infant formulas were derived from cow's milk or soybeans. In general, both types of infant formula had very low concentrations of CDDs. 2,3,7,8-TCDD and PeCDD were not detected in cow's milk or soybean formula at detection limits ranging from 0.5 to 1.0 ppt. HxCDD was not detected in soybean formula at the same detection limits. Whole and lowfat (2% fat) cow's milk contained total HxCDD at lipid-adjusted concentrations of 3.6 and 3.3 ppt, respectively. Lipid-adjusted levels of HpCDD were found in whole cow's milk formula (6.5 ppt), lowfat (2%) cow's milk formula (8 ppt), and soybean formula (2.3–3.0 ppt). OCDD was the most abundant congener in both cow's milk and soybean formula. Concentrations of OCDD (lipid-adjusted) were as follows: cow's milk formula (15 ppt), low fat (2%) cow's milk formula (21 ppt), and soybean formula (21–36 ppt) (Schecter et al. 1989c).

In comparison, a study by LaFleur et al. (1990) reported the concentration of 2,3,7,8-TCDD and 2,3,7,8-TCDF in whole milk and half and half. These authors also measured the additional exposure that resulted from migration of these compounds from bleached paperboard containers into the milk over various storage periods. The concentrations of 2,3,7,8-TCDD in whole milk ranged from 24 to 25 pg/kg and in half-and-half ranged from 13 to 14 pg/kg. The corresponding concentrations of 2,3,7,8-TCDF ranged from 260 to 280 pg/kg for whole milk and 146 to 195 pg/kg for half and half. These authors also determined the concentration of 2,3,7,8-TCDD and TCDF for cow’s milk obtained directly from a dairy and for milk stored for various time periods in bleached paperboard cartons. On a lipid basis, the concentration of 2,3,7,8-TCDD of control milk obtained directly from the dairy was 0.48 pg/g, and milk stored in paperboard cartons for 24, 48, 120, and 288 hours was 0.95, 1.4, 1.9, and 2.7 pg/g, respectively. The 2,3,7,8-TCDD and 2,3,7,8-TCDF concentrations in the paperboard carton were 4.3 and 25 ppt, respectively. Concentrations of 2,3,7,8-TCDF in the control milk was not detectable, but increased in milk stored in cartons for 24, 48, 120, and 288 hours to 6.8, 10.2, 20.1, and 35.1 pg/g, respectively. The percent migration of the 2,3,7,8-TCDD ranged from 2 to 6%, while the percentage of migration of the 2,3,7,8-TCDF ranged from 4 to 18% over the same period (LaFleur et al. 1990).

Similar levels of CDD contamination were reported in two European studies. CDDs were detected in 8 samples of cow's milk in Germany at concentrations ranging from 0.2 ppt for 2,3,7,8-TCDD (detection limit 0.2 ppt) to <10 ppt of OCDD (detection limit not significantly higher than blanks) (Beck et al. 1987). In a Swedish study, only 1 of 10 samples of milk held in either glass bottles or paper cartons contained a detectable level of 2,3,7,8-TCDD (0.46 pg/g milk fat; paper carton; detection limit 0.4 pg/g). Other CDDs were also detected (maximum 7.8 pg/g for OCDD) with the highest concentrations associated with milk packaged in paper cartons, indicating that leaching of CDDs from the paper carton into the milk can occur (Rappe et al. 1990).

Fish and Wildlife. A survey of 2,3,7,8-TCDD contamination in benthic (bottom feeding) and predator fish from major U.S. watersheds was conducted for the EPA National Dioxin Study (Kuehl et al. 1989). It was observed that 17 of 90 (19%) samples collected at sites statistically selected by the EPA had detectable levels of 2,3,7,8-TCDD, whereas 95 of 305 (31%) samples from sites chosen by EPA regional laboratories had detectable levels (detection limits 0.5–2 ppt on a wet weight basis). Of the 112 sites where 2,3,7,8-TCDD was detected, 74 samples (67%) were below 5 ppt, 34 samples (32%) were between 5 and 25 ppt, and 4 samples (1%) were above 25 ppt. A subset of samples collected at sites near the discharges from pulp/paper manufacturing facilities (n=28) had a higher frequency of 2,3,7,8-TCDD contamination above 5 ppt (38%). This subset of samples also contained the sample with the highest level of 2,3,7,8-TCDD contamination (85 ppt). Of the 29 samples collected in the Great Lakes region, 23 (79%) of the sites were found to have detectable levels of 2,3,7,8-TCDD. The most highly contaminated sample, with a concentration of 41 ppt, was collected from Lake Ontario near Oswego, NY. Four of 57 (7%) estuarine or coastal sites had detectable 2,3,7,8-TCDD levels in either fish or shellfish. The level of contamination in these 4 samples ranged from 1.08 to 3.5 ppt (Kuehl et al. 1989). In another study, fish sampled downstream from a bleached kraft paper mill were found to contain higher concentrations of CDDs compared with fish sampled upstream of the paper mill (Hodson et al. 1992). TCDD concentrations in the fish ranged from 1.47 pg/g (wet weight basis) in upstream areas to 15.6 pg/g in fish sampled 2 km downstream. Fish sampled 95 km downstream contained only about half the residues (8.87 pg/g TCDD) of those collected immediately downstream of the facility (Hodson et al. 1992).

Travis and Hattemer-Frey (1991) analyzed data collected as part of the National Dioxin Study regarding 2,3,7,8-TCDD concentrations in fish. The TCDD levels measured in fish from lakes and rivers in the United States confirm that 2,3,7,8-TCDD is bioaccumulating in fish and that low-level contamination of fish is widespread (EPA 1987n). The fish survey included 304 urban areas in the vicinity of population

centers or areas with known commercial fishing activity, including sites in the Great Lakes region. The results of this study indicate that only 29% of fish fillets collected at urban sites had detectable concentrations of 2,3,7,8-TCDD (detection limit =1 ppt). The geometric mean for these fillet samples was 0.3 ppt (wet weight basis). Fish samples from the Great Lakes area contained higher concentrations of 2,3,7,8-TCDD than fish from urban areas (e.g., 67 versus 29% contained detectable levels, respectively). In the Great Lakes area, the geometric mean concentrations of 2,3,7,8-TCDD in fish fillets (2.3 ppt) was almost 7 times higher than the concentrations in the fillets from fish collected from urban areas (0.3 ppt). Comparable concentrations of 2,3,7,8-TCDD were detected in bottom-feeding and predator species from the Great Lakes region. Approximately 74% of the fish fillet samples collected from sites near pulp and paper mills contained detectable concentrations of 2,3,7,8-TCDD. The geometric mean concentration for these fillet samples was 0.9 ppt. This geometric mean is 3 times higher than for urban fillet concentrations (0.3 ppt) but is approximately 2 times lower than for TCDD concentrations in fillets from the Great Lakes Region (2.3 ppt).

From 1986 to 1989, the National Study of Chemical Residues in Fish (NSCRF) was conducted by the EPA as a follow-on study to the National Dioxin Study (EPA 1992). The purpose of the NSCRF was to assess the concentrations of 60 toxic pollutants (including CDDs and CDFs) in the tissues of benthic and game fish nationwide. Benthic species were analyzed as whole-body samples, while game species were analyzed as fillet samples and all concentrations were on a wet weight basis. A summary of the prevalence and concentrations of 6 CDDs and 9 CDFs detected at 388 sites surveyed nationwide in the NSCRF is presented in Table 5-8. Four of the CDDs and three of the CDFs analyzed were detected at over 50% (58–89%) of the sites surveyed. The most frequently detected CDD/CDF compounds (1,2,3,4,6,7,8-HpCDD and 2,3,7,8-TCDF) were both found at 89% of the sites. These compounds were also detected at the highest concentrations: 1,2,3,4,6,7,8-HpCDD at 249 ppt and 2,3,7,8-TCDF at 404 ppt (wet weight). The mean concentrations of these 2 compounds were substantially lower at 10.5 and 13.6 ppt, respectively. The CDD (2,3,7,8-TCDD) believed to be the most toxic congener to mammals, was found at 70% of the sites at a maximum concentration of 204 ppt and a mean of 6.8 ppt (wet weight basis). The NSCRF report further shows that pulp and paper mills using chlorine bleach pulp appeared to be the dominant source of the 2,3,7,8-TCDD and 2,3,7,8-TCDF. Fish collected at sites downstream of pulp and paper mills had significantly higher concentrations of 2,3,7,8-TCDD than fish collected near all other source categories. The statistical tests also showed the same result for 2,3,7,8-TCDF, with the exception that fish residue concentrations downstream of Superfund sites also marginally met the statistical criteria. With respect to source categories, the NSCRF data showed that fish collected downstream of pulp and paper mills (using

Table 5-8. Summary of CDDs/CDFs Detected in Fish Tissue as Part of the EPA National Study of Chemical Residues in Fish[a]

Congener	% Sites where detected	Maximum	Mean	Standard deviation	Median
2,3,7,8-TCDD	70	203.6	6.89	19.41	1.38
1,2,3,7,8-PeCDD	54	53.95	2.38	4.34	0.93
1,2,3,4,7,8-HxCDD	32	37.56	1.67	2.39	1.24
1,2,3,6,7,8-HxCDD	69	100.9	4.30	9.25	1.32
1,2,3,7,8,9-HxCDD	38	24.76	1.16	1.74	0.69
1,2,3,4,6,7,8-HpCDD	89	249.1	10.52	25.30	2.83
2,3,7,8-TCDF	89	403.9	13.61	40.11	2.97
1,2,3,7,8-PeCDF	47	120.3	1.71	7.69	0.45
2,3,4,7,8-PeCDF	64	56.37	3.06	6.47	0.75
1,2,3,4,7,8-HxCDF	42	45.33	2.35	4.53	1.42
1,2,3,6,7,8-HxCDF	21	30.86	1.74	2.34	1.42
1,2,3,7,8,9-HxCDF	1	0.96[b]	1.22	0.41	1.38
2,3,4,6,7,8-HxCDF	32	19.3	1.24	1.51	0.98
1,2,3,4,6,7,8-HpCDF	54	58.3	1.91	4.41	0.72
1,2,3,4,7,8,9-HpCDF	4	2.57	1.24	0.33	1.30
EPA-TEQ[c]	NA	213	11.1	23.8	2.80

[a] Concentrations are picograms per gram (pg/g) or parts per trillion (ppt) by wet weight. The mean, median, and standard deviation were calculated using one-half the detection limit for samples which were below the detection limit. In cases where multiple samples were analyzed per site, the value used represents the highest concentration.

[b] Detection limits were higher than the few quantified values for 1,2,3,4,7,8,9-HpCDF and 1,2,3,7,8,9-HxCDF. Maximum values listed are measured values.

[c] This EPA study did not analyze concentrations of octachlorodibenzo-*p*-dioxin or octachlorodibenzofurans in fish tissues; this TEQ value does not include these two compounds.

CDDs = chlorinated dibenzo-*p*-dioxins; CDFs = chlorinated dibenzofurons; EPA = Environmental Protection Agency; HpCDD = heptachlorodibenzo-*p*-dioxin; HpCDF = heptachlorodibenzofuran; HxCDD = hexachlorodibenzo-*p*-dioxin; HxCDF = hexachlorodibenzofuran; NA = not applicable; PeCDD = pentachlorodibenzo-*p*-dioxin; PeCDF = pentachlorodibenzofuran; TCDD = tetrachlorodibenzo-*p*-dioxin; TCDF = tetrachlorodibenzofuran; TEQ=Toxicity equivalency concentration

Source: EPA 1992

chlorine bleaching processes) had the highest median 2,3,7,8-TCDD concentrations (5.66 ppt), compared to the next highest source category, refinery/other industrial sites (1.82 ppt), industrial/urban sites (1.40 ppt), Superfund sites (1.27 ppt), and background sites (0.5 ppt). Source categories with the highest 2,3,7,8-TCDD concentrations in fish also had the highest TEQ values. OCDD and OCDFs were not analyzed in tissue because at the time the NSCRF study was initiated (1986), the TEFs were zero for these compounds. In 1989, TEFs for OCDD and OCDFs were increased to 0.001. Consequently, TEQ values presented in the NSCRF report may be underreported for samples collected at sites with sources of OCDD/OCDFs (e.g., wood preservers) (EPA 1992).

De Vault et al. (1989) collected samples of lake trout and walleye for CDD and CDF analysis from each of the Great Lakes and Lake St. Clair. One of the conclusions of the National Dioxin Study was that fish from the Great Lakes region were among the most severely contaminated in the United States. Fish were analyzed for 8 congeners of CDDs and 10 congeners of CDFs. Total CDD concentrations ranged from 7.2 ng/kg in lake trout from Lake Superior to 64.5 ng/kg in Lake Ontario (wet weight basis). Concentrations of 2,3,7,8-TCDD ranged from 1 ng/kg in lake trout from Lake Superior to 48.9 ng/kg in lake trout from Lake Ontario. The dominant congener in all but Lake Ontario was 1,2,3,7,8-PeCDD at concentrations ranging from 2.3 ng/kg in Lake Superior to 16.7 ng/kg in Lake Michigan. The only other congener that significantly contributed to the total CDD concentration was 1,2,3,6,7,8-HxCDD, which ranged from 1.3 ng/kg in Lake Superior to 10.9 ng/kg in Lake Michigan. Substantial interlake differences exist in the percentage of total CDD contributed by the various congeners. The 2,3,7,8-TCDD congener contributes a relatively small percentage of the total CDD in fish from Lakes Superior, Michigan, and Erie. It is comparatively more important in Lake Huron (32%) and Lake St. Clair (36%) and contributes 76% of the total CDD in Lake Ontario. The results of this study support the widespread contamination of the Great Lakes ecosystem and clearly show that both the concentration of individual congeners and the congener composition of total CDDs in Great Lakes fish vary significantly between lakes and in Lake Michigan between sites. The authors suggest that these differences may be associated with different sources and loadings of these compounds to each of the Great Lakes (De Vault et al. 1989). This is confirmed by the analysis of sources of CDDs in the Great Lakes which appear to be both from atmospheric deposition and industrial point sources (Hebert et al. 1994).

In another study, CDDs and CDFs were measured in four species of salmonids (coho salmon, lake trout, rainbow trout, and brown trout) collected from Lake Ontario (Niimi and Oliver 1989a). Total CDD concentrations ranged from 46 to 290 ng/kg (ppt) in whole fish and 60–366 ng/kg in muscle composite

samples. Levels of 2,3,7,8-TCDD in whole fish ranged from 60–20 ppt (wet weight basis). This represented 60% of total TCDDs and 10% of total CDDs. The HxCDD congener group was most dominant in all fish species and represented approximately 39% of the total CDD concentrations. High concentrations of OCDD were also detected in coho salmon (160 ng/kg whole fish and 280 ng/kg muscle) and lake trout (89 ng/kg whole fish and 28 ng/kg muscle) but not in brown or rainbow trout. The authors could not explain this difference; however, OCDD is typically the CDD present at the highest concentrations in Lake Ontario water, suspended sediments, and sediments. Although the total CDF concentrations were 75% lower than the total CDD concentrations, the levels of 2,3,7,8-TCDF (11–20 ppt) were comparable to levels of 2,3,7,8-TCDD (6–20 ppt). Results of another study by the same authors found that TEQ values for PCB concentrations in Lake Ontario salmonids were several fold higher than TEQ values for CDDs and CDFs in the same fish species (Niimi and Oliver 1989b).

Background concentrations of CDDs in fish were measured in the Mississippi River and Lake Orono in Elk River, Minnesota, a semi-rural location (Reed et al. 1990). No major industrial or commercial activity occurred in the area at the time of the study, and the survey was conducted as a baseline study prior to the operation of the Elk River Electric Generating Station (powered by refuse-derived fuel). None of the fish collected contained measurable amounts of 2,3,7,8-TCDD; however, one of the composites from the Mississippi River contained 3.9 ppt of total TCDD (wet weight basis). Detection limits ranged from 0.28 ppt to 6.6 ppt on a congener-specific and sample-specific basis and were not individually reported for each result. OCDD was the most abundant congener (average 59 ppt, range 56–62 ppt), followed in decreasing order by total HpCDD (average 19.3, range 15–22 ppt), total HxCDD (average 6.87 ppt, range 2.3–11 ppt), and total PeCDD (average 3.9 ppt, range 3.5–4.5 ppt) (Reed et al. 1990). Lake Orono showed the same pattern, with OCDD being the most abundant congener (average 39 ppt, range 35–43 ppt), followed by total HpCDD (average 10.5, range 10–11 ppt), and total HxCDD (3.0 ppt). PeCDDs were not detected in the Lake Orono samples (Reed et al. 1990).

Contamination of the Spring River in southwest Missouri by 2,3,7,8-TCDD is believed to have resulted from several well defined point-source waste disposal sites (Crunkilton et al. 1987). Analysis of 31 fish samples (11 different fish species) collected from 1981 to 1983 demonstrated a rapid decline in 2,3,7,8-TCDD concentrations in fish at increasing distances both upstream and downstream from the area of contamination. Mean concentrations of 2,3,7,8-TCDD 0.5 km downstream from the area of contamination were 38 ppt in whole fish and 20 ppt in fish fillets (wet weight basis). Mean concentrations in fish

caught more than 14 km downstream were below 4 ppt in both whole fish and fillet samples (Crunkilton et al. 1987).

Fish samples (butterfish, flounder, hake, and herring) collected in 1984 from the Atlantic Ocean off Long Branch, NJ, contained no detectable levels of 2,3,7,8-TCDD (detection limit <10 pg/g) (wet weight basis) (Firestone et al. 1986). Cod caught in the northwest Atlantic in November 1990 did not have detectable levels of any CDDs in their muscles or ovaries, although 5 of 10 liver samples had OCDD at a mean concentration of 0.8 ppt and TCDD was found in 3 of 10 samples at 0.1 ppt (Hellou and Payne 1993). A 4-year study of marine and freshwater fish and other edible aquatic organisms taken from Canadian waters that received effluents from pulp and paper mills indicated that 2,3,7,8-TCDD was the most prominent CDD found in the fish regardless of the tissue sampled or sampling location. The maximum 2,3,7,8-TCDD concentration detected in the edible organisms sampled was for crab hepatopancreas tissue (>500 pg/g) (wet weight basis). Whole fish samples also contained greater CDD concentrations than fillet samples (Whittle et al. 1993).

Several studies have been conducted to monitor 2,3,7,8-TCDD concentrations in fish and shellfish in northern New Jersey in the vicinity of a pesticide manufacturing site that allegedly released an estimated 4–8 kg of 2,3,7,8-TCDD over a 20-year period (Bopp et al. 1991). Samples of striped bass, blue crabs, and lobsters collected from Newark Bay and the New York Bight (marine waters directly offshore from New York Harbor) all contained high concentrations (up to 6,200 ppt) (wet weight basis) of 2,3,7,8-substituted TCDD, PeCDD, and CDFs (Rappe et al. 1991). Concentrations of HxCDD and HpCDD ranged from <0.1 to 220.7 ppt and <0.7 to 244.9 ppt, respectively. The concentrations of 2,3,7,8-TCDD in these marine organisms were higher than any other New Jersey samples and represented the highest concentrations of 2,3,7,8-TCDD reported for aquatic species. The two crustaceans sampled in the study had similar congener patterns; they all contained both a large number and large amounts of CDD and CDF congeners in addition to the 2,3,7,8-substituted chlorinated compounds. In contrast, the striped bass samples contained primarily the 2,3,7,8-chlorine-substituted congeners. The concentrations of 2,3,7,8-TCDD in crab hepatopancreas tissue ranged from 3,700 to 6,200 ppt and from 100 to 120 ppt in crab meat. Concentrations of 2,3,7,8-TCDD were lower in the lobster, ranging from 250 to 610 ppt in the hepatopancreas and 5 to 6 ppt in the meat. Concentrations of 2,3,7,8-TCDD in striped bass muscle tissue ranged from 84 to 730 ppt. In this study, the crustacean samples all contained very complex ion curves for the TCDDs showing 10 major and 5 minor peaks, while the striped bass samples primarily contained the 2,3,7,8-TCDD isomer and a few other isomers. With respect to the PeCDDs, the crustacean samples

contained 5–6 peaks including the 1,2,3,7,8-PeCDD (100 ppt in hepatopancreas and 1–2 ppt in meat), while the major isomer found in the striped bass was 1,2,3,7,8-PeCDD (5–10 ppt). Regarding the HxCDDs, the crustacean samples contained 3 major peaks one of which was 1,2,3,6,7,8-HxCDD (100–300 ppt in the hepatopancreas); while the striped bass samples contained concentrations <1 ppt. The HpCDD congeners (1,2,3,4,6,7,9- and 1,2,3,4,6,7,8-) were detected in crustacean hepatopancreas tissue ranging from 31.7 to 411.9 ppt, while meat samples contained 0.00-8.5 ppt. Striped bass tissue samples contained 4–11.4 ppt. Concentrations of OCDD ranged from 50.5 to 94.6 ppt in crustacean hepatopancreas tissues, 6.3–78.8 ppt in meat samples, while concentrations in striped bass ranged from 5.1–49.5 ppt (Rappe et al. 1991).

Cai et al. (1994) analyzed blue crab tissue (hepatopancreas and muscle) from Newark Bay and some adjacent areas of the New York Bight for 2,3,7,8-TCDDs and 2,3,7,8-TCDF and several other 2,3,7,8-substituted CDDs/CDFs. These authors found 2,3,7,8-TCDD concentrations in hepatopancreas tissue to be 10–20 times higher than muscle concentrations. Lipid content of the hepatopancreas is 6–9% as compared to 1% for muscle tissue. The highest concentration of CDDs/CDFs was detected in crabs collected at the station closest to the pesticide production facility. Crabs also had higher CDDs/CDF concentrations in September after feeding all summer than crabs collected in June. Concentrations of 2,3,7,8-TCDD up to 1 ppb were detected in some crabs collected from Newark Bay (detection limit 0.5–1 ppt). Hauge et al. (1994) conducted further studies of blue crabs and lobsters from three distinct fisheries in the Hudson-Raritan estuary. The Ambrose fishery includes Raritan and Sandy Hook Bays and extends to a 7-nautical-mile radius from Ambrose Light near the entrance to New York Harbor. The Alongshore fishery is a box-shaped area extending from Long Branch, NJ, south to Point Pleasant, NJ, and then extending off-shore approximately 25 nautical miles. The Offshore fishery extends eastward from the 50-fathom line to the 100-fathom line approximately 100 miles seaward to the edge of the continental shelf. Combined muscle/hepatopancreas samples of blue crabs from Raritan Bay and the lower Hudson River had a mean 2,3,7,8-TCDD concentration of 71.5 pg/g (range not detected to 260 pg/g) and a mean 2,3,7,8,-TCDF concentration of 67.1 pg/g (range not detected to 110 pg/g). The mean total TEQ concentration was 78.2 pg/g (ppt) (wet weight basis). Both the mean 2,3,7,8-TCDD concentration and the mean TEQ values exceeded the FDA guidelines for "no consumption" (>50 ppt) (see Chapter 7). FDA “no consumption” guidelines advise consumers that fish and shellfish should not be consumed when CDD concentrations exceed 50 ppt. 2,3,7,8-TCDD and TCDF were detected in 53 and 67% of crabs, respectively. Levels of 2,3,7,8-TCDD in muscle and hepatopancreas of lobsters were similar in animals from the Ambrose and Alongshore fisheries, with the mean concentration in both areas ranging from 34 to

41 pg/g of 2,3,7,8-TCDD/TCDF. The mean total TEQ values were 38.5 pg/g (Ambrose fishery) and 44.4 pg/g (Alongshore fishery). Mean 2,3,7,8-TCDD/TCDF levels thus exceeded the FDA "safe consumption" level (#25 ppt), but did not exceed the FDA "no consumption" level (>50 ppt). None of the lobsters from the Offshore fishery contained detectable TCDD/TCDF. Analysis of separate muscle and hepatopancreas tissues from individual lobsters yielded detectable concentrations of both contaminants only in the hepatopancreas (<26–410 pg/g for 2,3,7,8-TCDD and <33–380 pg/g for 2,3,7,8-TCDF). Concentrations in lobster muscle tissues were all below detection limits of 6–20 pg/g for 2,3,7,8-TCDD and 10–25 pg/g for 2,3,7,8-TCDF.

Concentrations of CDDs/CDFs were also evaluated in a bivalve mollusc, the soft-shelled clam *(Mya arenaria)* in Newark Bay, Arthur Kill, and Raritan Bay (Brown et al. 1994). Clams from Newark Bay contained 11–20 ppt TCDD, 3.5–5 ppt TCDF, and 13–25 ppt TEQ; those from Arthur Kill contained 4.8–7.7 ppt TCDD, 3.1–5.1 ppt TCDF, and 6.8–11 ppt TEQ; and those from Raritan Bay contained 0.5–1.1 ppt TCDD, 2–4.6 ppt TCDF, and 1.2–2.1 ppt TEQ (wet weight basis). The maximum TEQ concentration of the Newark Bay clams (25 ppt) approached the upper limit of the FDA "safe consumption" level of #25 ppt. The FDA believes that consumption of fish or shellfish with CDD concentrations #25 ppt should not result in any serious health effects. Concentrations decreased with increasing distance from the suspected pesticide plant site near Newark Bay. The authors also showed that the clams could eliminate TCDD and TCDF when they were removed to clean water sites. The half-lives of the TCDD, TCDF, and TEQ were calculated to be 45, 111, and 66 days, respectively.

Concentrations of CDDs and CDFs were also reported in wood ducks (*Aix sponsa*), species of migratory waterfowl collected near Bayou Meto, Arkansas (White and Hoffman 1995). The EPA identified a former 2,4,5-T chemical manufacturing plant as the source of the contamination and subsequently listed the areas on the NPL of hazardous waste sites in 1982. Residues in wood duck eggs based on 2,3,7,8-TCDD (TEQs) ranged up to 611 ppt, and the egg arithmetic means were 90-fold higher at the site nearest the point source discharge compared to the reference site. The State of Arkansas has issued a wildlife consumption advisory for wood ducks in the Bayou Meto area (EPA 1998).

CDDs were determined in pooled samples of ringed seal *(Phoca hispida)* blubber, beluga whale *(Delphinapterus leucas)* blubber, and polar bear *(Ursus maritimus)* liver and fat collected from several areas throughout the Canadian north (Norstrom et al. 1990). All seal samples and all but one polar bear sample had detectable levels of 2,3,7,8-TCDD (wet weight) ranging from 2 to 37 ppt, but 2,3,7,8-TCDD was not

found in beluga blubber (<2 ppt). All seal samples and one of the three beluga whale samples contained 2,3,7,8-TCDF (2-7 ppt), but 2,3,7,8-TCDF was not found in polar bear samples. OCDD concentrations in seal blubber and polar bear samples ranged from not detected (<8 ppt) to 43 ppt. No biomagnification of TCDD and OCDD occurred from seal to bear fat. The highest concentrations of 2,3,7,8-TCDD and OCDD in seals and bears were found in the central Canadian Arctic Archipelago, and the lowest concentrations were found in the Hudson Bay area. The reason for higher concentrations of 2,3,7,8-TCDD and OCDD in the Arctic than in sub-Arctic areas is thought to be transpolar movement of aerosols from combustion-related sources originating in Eurasia (Norstrom et al. 1990). CDDs and CDFs were determined in caribou tissue samples from 7 herds across the Canadian Arctic (Hebert et al. 1996). In contrast to marine mammals, concentrations for caribou were extremely low, sub-ng/kg (lipid basis), for all congeners except OCDD and 1,2,3,7,8-PeCDD in one herd. OCDD was found in most of the samples at concentrations ranging from < 0.2 ng/kg in fat to 4.7 ng/kg in adipose tissue. The one pooled liver sample analyzed from the Yukon had an OCDD concentration of 11 ng/kg (lipid basis). 2,3,7,8-TCDD was detected in adipose tissue samples of two herds in the eastern Canadian Arctic at levels of 0.73 and 0.14 ng/kg, but was not detected in tissue samples from other herds at detections limits as low as 0.03 ng/kg (lipid basis). CDF levels were sub-ng/kg in all cases. TEQs were dominated by non-ortho substituted PCBs in all cases, and ranged from 0.33 ng/kg to 3.29 ng/kg in adipose tissue. The authors concluded that caribou tissues are therefore less contaminated than tissues from marine mammals.

Consumer products.

Cigarettes and Cigarette Smoke. CDDs have been detected in cigarettes and cigarette smoke. In a recent study, Lofroth and Zebuhr (1992) detected CDD/CDF concentrations in both mainstream (collected directly on a glass fiber filter) and sidestream smoke (emitted into an acrylic box and then collected on a glass fiber filter) from a single brand of commercially available Swedish cigarettes. These authors reported that the mainstream smoke from 20 cigarettes contained about 18 pg TEQ (1 pg TEQ per cigarette), while sidestream smoke contained 39 pg TEQ (2 pg TEQ per cigarette). No particular isomer contributed more than 20% to the total TEQ value. Most isomers were not present at concentrations above the detection limits (0.3–1.3 pg), with the exception of 1,2,3,4,6,7,8-HpCDD (6.8 pg), 1,2,3,4,6,7,8-HpCDF (4 pg), and OCDD (7.3 pg). An earlier study that used low-resolution mass spectrometry for analysis of CDDs in cigarette smoke obtained by a continuous smoking process (all cigarette tobacco gave rise to mainstream smoke) found that HpCDD was the most abundant homologue detected, accounting for >90% of the total CDDs (Muto and Takizawa 1989).

Paper Products. CDDs are formed during pulp bleaching, and as a result they have been found in many different types of paper products. 2,3,7,8-Substituted CDDs were determined in different samples of coffee-filter paper (Beck et al. 1988b, 1989d). 2,3,7,8-TCDD was the most abundant congener detected at a mean concentration of 3.85 ppt (range 1.6–7.3 ppt). OCDD was detected at a mean concentration of 2.05 ppt (range 0.7–3.5 ppt). PeCDDs, HxCDDs, and HpCDDs were identified at concentrations ranging from 0.03 to 0.7 ppt. In an earlier study, HxCDD was the most abundant homologue detected in coffee filters (2.1 ppt) and 2,3,7,8-TCDD was found at concentrations of 1 ppt (Beck et al. 1988b). Coffee brewed without filters did not contain any detectable CDDs; however, coffee brewed with one filter showed leaching of TCDDs from the paper into the coffee. Carryover (leaching) rates were 25% for 2,3,7,8-TCDD, indicating that people who drink coffee brewed with paper filters containing 5 ppt 2,3,7,8-TCDD may ingest small quantities (<5 pg) of 2,3,7,8-TCDD per day (Beck et al. 1989d). Hashimoto et al. (1992) also analyzed CDD/CDF concentrations in coffee-filter paper available in Japan. These authors reported mean TEQ values of 0.89 pg/g (ppt) (range 0.042–3.6 pg/g) for chlorine-bleached filters, 0.13 pg/g (range 0.079–0.18 pg/g) for oxygen-bleached filters, and 0.009 pg/g (range 0.00038–0.017 pg/g) for unbleached filters. Chlorine-bleached filters also gave the highest mean TCDD and TCDF elutions (range <0.043–2.1 and <0.081–6 pg/g, respectively). Oxygen-chlorinated filters gave considerably lower elutions (range <0.085–0.14 and 0.23–0.26 pg/g, respectively), while unbleached filters produced elutions near the detection limits (<0.094 pg/g). Approximately one-third of the total CDD/CDF contamination was eluted from the filter paper into the coffee during brewing; however, almost the same amount was eluted from the filters with hot water. This leaching rate of approximately 30% agrees with that obtained by Beck et al. (1989d). The elution ratio was almost constant for all CDD/CDF congeners and isomers. Using the maximum TEQ value of 3.6 pg/g paper and the minimum TEQ value of 0.00038 pg/g paper, the TEQ values for one cup of coffee were calculated to range from 0.000015 pg to 1.4 pg. The authors suggest that any potential health risk from CDD/CDF exposure from coffee-filter paper is small and can be further reduced by rinsing the filter prior to brewing the coffee.

CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) are also present in newsprint, facial (cosmetic) tissue, and recycled paper at levels ranging from <0.4 to 335 ppt (Beck et al. 1988b). OCDD was the most abundant congener detected in newsprint (37 ppt). HxCDD was the most abundant homologue detected in cosmetic tissue (79 ppt) and recycled paper (335 ppt). 2,3,7,8-TCDD was found at lower concentrations in cosmetic tissue (1.1 ppt), and recycled paper (0.6 ppt) (Beck et al. 1988b). Another study of CDDs in bleached and unbleached consumer paper products showed that the highest levels of 2,3,7,8-TCDD were found in bleached coffee filters (5 ppt), unbleached coffee filters (2.0 ppt), bleached shopping bags

(1.3 ppt), and cigarette paper (1.4 ppt) (Wiberg et al. 1989). Concentrations were found to be lower in the unbleached products than in the corresponding bleached products (Wiberg et al. 1989). 2,3,7,8-TCDD has been measured in tea bags at concentrations ranging from not detected (0.36 ppt) to 4.79 ppt (Sullivan and Stanford 1990).

The use of newsprint for cow bedding was examined to determine if CDDs in the newsprint would find their way into the cow's milk as a result of the cow's ingesting its bedding. Although HxCDD and OCDD were detected in the milk, TCDD was not detected (detection limit 0.5 ppt) (Shane et al. 1993).

Ryan et al. (1992) analyzed the concentrations of CDDs/CDFs in Canadian bleached-paper milk containers from 1988 to 1989 and examined the resulting concentrations transferred to the milk. Milk-carton paper manufactured prior to 1989 tested positive for 2,3,7,8-TCDF and 2,3,7,8-TCDD, with levels on a TEQ basis varying between 1.4 and 55 ng/kg of paper. Bleached milk-carton paper produced after mid-1989 tested negative for these compounds at a limit of detection of 1 ng/kg paper. Storage of 3 types of milk in the pre-1989 low- and high-level cartons resulted in the transfer of the TCDD/TCDF into the milk, most of which occurred within the first 7 days. The TCDD/TCDF transfer varied between 3 and 25%, with whole and 2% fat milk accumulating about twice the concentrations of skim milk. On the basis of these results, milk stored for up to 14 days at 5 EC in currently produced bleached-paper containers with less than 1 ng TEQ/kg of paper would not contain any detectable CDDs/CDFs (<0.005 ng TEQ/kg milk).

An FDA study of the migration of TCDD from paper products that come in contact with food found that TCDD was present in all paper products at concentrations ranging from 0.5 ppt for coated paper trays to 13 ppt for coated paper cups (average 2–8.5 ppt). Migration of TCDD from the paper into the food ranged from below detectable limits for coated juice cartons to 24% for coffee filters. Most CDDs migrated in the range of 4–8%. The TEQ estimated concentration values ranged from 1.5 ppt for coffee filters to 140 ppt for paper plates (Cramer et al. 1991).

LeBel et al. (1992) analyzed a wide variety of paper products purchased from retail stores in Canada in 1988 and 1991 for TCDD/TCDF through OCDD/OCDF. The congeners exhibiting the highest concentrations in most paper products were 2,3,7,8-TCDF, OCDD, and 2,3,7,8-TCDD. With respect to the TEQ values, the mean TEQ for disposable diapers increased from 1.4 to 2.0 pg/g from 1988 to 1991. The TEQ values decreased during the same period for facial tissues (5.2–4.0 pg/g), paper plates (6.4–2.2 pg/g), paper cups (22.7–10.5 pg/g), and coffee filters (3.7–0.1 pg/g). The CDD/CDF concentrations found in

coffee filters in 1988 were similar to concentrations reported in the United States (Cramer et al. 1991) and in Germany (Beck et al. 1988b). The authors cautioned that, given the small number of both paper products and samples analyzed, these data do not permit them to draw any conclusions regarding trends in CDDs/CDF levels in paper products.

Dyes and Pigments. Malisch (1994) reported the presence of CDDs/CDFs in colored candle wax produced with the dye pigment Violet 23, which is derived from chloranil. The three candle samples with the highest contamination contained 1.8, 1.4, and 0.8 ng TEQ/kg (ppt). The author also noted that candles of the same color could have highly different CDD/CDF concentrations based on the composition of dye pigments used in the manufacturing process.

Three pigments used in fabric dyeing that are derived from chloranil include the dioxazine pigments Violet 23 and Direct Blue 106 and 108 (Williams et al. 1992). Concentrations of the congeners OCDD and OCDF predominated in the pigment Blue 106 and ranged from 18,066 to 41,953 ng/g (ppb) for OCDD and 1,006–12,463 ng/g (ppb) for OCDF. Pigment Blue 108 contained much lower concentrations of CDDs/CDFs, although OCDD and OCDF were also the predominant congeners detected at 23 and 11 ng/g, respectively. Violet 23 contained higher CDD/CDF concentrations than Direct Blue 108 but lower concentrations than Direct Blue 106. OCDD concentrations ranged from 806 to 11,022 ng/g (ppb), while OCDF concentrations ranged from 125 to 3,749 ng/g (ppb). The TEQ values for Direct Blue 106, Direct Blue 108, and Violet 23 were 35.4, 0.1, and 9.1 ng/g (ppb), respectively.

Textile Products. A recent study has identified sources of CDDs/CDFs found in textiles. Horstmann and McLachlan (1994a) detected CDD/CDF concentrations in new textile products ranging from less that 50 pg/g to as high as 290,000 pg/g. The authors believe that textile finishing processes are not the source of the high CDD/CDF concentrations because of the randomness of the textiles with high concentrations. Since PCP is still being used in developing countries, especially for purposes of preserving cotton during sea transport, the authors hypothesize that this is a likely source.

Dry Cleaning Fluid Residues. Chemical analysis of dry cleaning solvent residues collected in Germany prior to 1993 indicated that residues from machines using perchloroethylene contained an average concentration of 256 ppb CDD/CDF, with 2,3,7,8-TCDD being detected in 21 of 28 samples; however, the HpCDD and OCDD congeners comprised between 90 and 95% of the CDDs/CDFs found (Towara et al. 1992). Horstmann and McLachlan (1994b) detected CDD/CDF residues in used dry cleaning fluid and

concluded that the source of the CDDs/CDFs residues in the dry cleaning fluid were introduced by dry cleaning new, unwashed textiles that had been treated with pentachlorophenol (PCP).

Motor Vehicle Exhaust. CDDs have also been identified in automobile exhaust emissions (Marklund et al. 1987, 1990). 2,3,7,8-TCDD was found in car exhaust from 4 Swedish cars running on leaded gasoline at levels ranging from <0.05 to 0.3 ng/24.8 km (0.002–0.01 ng/km) running cycle. PeCDD was also found in the exhaust of cars running on leaded gasoline at levels ranging from 6 to 98 ng/24.8 km (0.24–3.95 ng/km). No CDDs were found in samples where unleaded gasoline was used at detection limits of 0.05 ng (2,3,7,8-TCDD) and 0.3 ng (PeCDD) (Marklund et al. 1987). Another study of exhaust emissions from cars running on leaded and unleaded gasoline found total HpCDD concentrations ranging from not detected to 0.482 ng/km and OCDD concentrations ranging from not detected to <0.510 ng/km for the cars running on leaded gasoline (Bingham et al. 1989). HpCDD was not detected in car exhaust emissions from a single car running on unleaded gasoline. OCDD concentrations ranged from not detected to <0.110 ng/km (Bingham et al. 1989). Most recently, however, Cirnies-Ross et al. (1996) reported that using copper in diesel fuels to reduce soot generation in engines was accomplished at the expense of increasing CDD/CDF during combustion. These authors reported that using the copper doped fuel significantly increased CDD/CDF particulate formation from < 20 ng/L TEQ in normal fuel to almost 60 ng/L TEQ in doped fuel at an engine output of 1 kW. The increased CDD/CDF particulate formation was most striking at low engine output (1 kW).

From the research conducted on CDD emissions from vehicles running on leaded and unleaded gasoline, it is clear that CDD emissions are typically less in cars running on unleaded gasoline. It should be noted however, that because the use of leaded gasoline is no longer permitted in the vast majority of domestic automobiles in the United States, this source of CDD emissions to the air should have been significantly reduced in recent years (EPA 1996a).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

5.5.1 General Population

Currently, consumption of food (including human milk) is by far the most important pathway for exposure to CDDs for the general population representing over 90% of the total daily intake. Other pathways of exposure include inhalation of CDDs from municipal, medical, and industrial waste incinerators and other

incineration and combustion processes (~2% of the daily intake), and ingestion of drinking water(<0.1% of the daily intake) (Travis and Hattermer-Frey 1987; Schaum et al.1994).

Foods. Food is the major source (>90%) of human exposure to CDDs (Beck et al. 1989a; Hattemer-Frey and Travis 1989; Liem and van Zorge 1995; Rappe 1992; Schaum et al. 1994; Schecter et al. 1994d, 1994e, 1996a). An estimate of the daily intake of 2,3,7,8-TCDD by adults in the general U.S. population from ingestion of contaminated food items and drinking water and inhalation of ambient air is given in Table 5-9. The average daily adult intake of 2,3,7,8-TCDD estimated by the model was 47 pg/day (Hattemer-Frey and Travis 1989) with a lower bound daily intake of 8 pg/day and an upper bound daily intake of 300 pg/day. Food, especially meat, and dairy products, accounted for 98% of the total daily intake of 2,3,7,8-TCDD. Hattemer-Frey and Travis (1989) estimated that the average daily intake of 2,3,7,8-TCDD for an adult in the United States from meat alone was 23 pg/day, accounting for 50% of the total daily intake of 2,3,7,8-TCDD from food sources. The average daily intakes of 2,3,7,8-TCDD from milk, produce, and fish were 13 pg/day (27%), 5 pg/day (11%), and 5 pg/day (10%), respectively of the total daily intake in the United States (Hattemer-Frey and Travis 1989). However, for certain subpopulations (recreational and subsistence fishers), fish consumption may be a more important source of CDDs. The maximum daily intake of 2,3,7,8-TCDD for residents of the Great Lakes region who regularly consume fish from the Great Lakes was estimated to range from 390 to 8,400 pg/day (EPA 1985a). Inhalation of ambient air and ingestion of water are not major pathways of human exposure, accounting for only 2% (1 pg/day) and <0.01% (6.5×10^{-3} pg/day), respectively, of the total daily intake of 2,3,7,8-TCDD (Hattemer-Frey and Travis 1989). The percentage of daily intake of 2,3,7,8-TCDD estimated by Hattemer-Frey and Travis (1989) from each exposure pathway agrees closely with more recent estimates made by Schaum et al. (1994) for intakes of total CDDs/CDFs (Table 5-10). However, quantitatively, the estimates differ by a factor of 2–3 because Hattemer-Frey and Travis (1989) considered only 2,3,7,8-TCDD, while Schaum et al. (1994) based their estimates on all CDDs and CDFs.

Based on their congener-specific analysis of 18 food samples collected in Binghamton, New York, Schecter et al. (1994d), estimated the U.S. mean daily exposure to CDD equivalents for an adult (65 kg body weight) to range from 18 to 192 pg TEQs depending on how not-detected values were treated. This is equal to a daily adult intake of CDDs/CDFs ranging from 0.3 to 3.0 pg TEQs/kg body weight. These authors reported that total CDDs ranged from 0.35 to 2.91 ppt (wet weight) in fish, from 0.6 to 59.3 ppt in meat products, and from 0.6 to 14 ppt in dairy products. The total CDD/CDF TEQ value ranged from 0.023 to 0.13 ppt for fish, 0.03 to 1.5 for meat products, and 0.04 to 0.7 for dairy products. The authors

Table 5-9. Estimated Average Daily Intake of 2,3,7,8-TCDD by the General U.S. Population

Source/pathway	Daily intake (pg/day)	Percentage of total daily intake
Ambient sources (total)	**1.01**	**2**
Air/Inhalation	1	2
Water/Ingestion	6.5×10^{-3}	<.01
Soil/Ingestion	—	—
Food sources (total)/ Ingestion	**46**	**98**
Produce (fruits and vegetables)	5	11
Milk	13	27
Meat	23	50
Fish	5	10
Total intake	**47**	**100**

Source: Travis and Hattemer-Frey 1989

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Table 5-10. Estimated Daily Background Exposure to CDDs/CDFs in the General U.S. Population

Source	Daily intake (pg TEQ/day)	Percentage of total daily intake
Ambient Sources (total)	**3**	**2.5%**
Air	2.2	1.8
Water	0.008	0.01
Soil	0.8	0.7
Food (total)	**116**	**97%**
Produce (fruits and vegetables)	ND	ND
Milk and Milk Products	42	35
Milk	18	15
Cheese	24	20
Meat/Meat Products/ Eggs	66.1	55
Pork	12	10
Beef	37	30.8
Chicken	13	11
Eggs	4.1	3.4
Fish and Fish Oil	7.8	6.6
Total Exposure	**120**	**100%**

Source: Schaum et al. 1994

CDD = chlorinated dibenzo-*p*-dioxins; CDF = chlorinated dibenzofurans; ND = no data

reported that a vegetarian diet (vegan diet with no consumption of dairy products) might have health advantages by lowering daily intakes to only 2% of the level estimated for persons consuming fish, meat, and dairy products (Schecter et al. 1994d, 1984e). An ovo-lacto vegetarian diet that contains eggs and dairy products would not achieve this same reduction level. More recently, these same authors estimated the U.S. mean daily exposure to CDD equivalents based on an expanded analysis of 100 food samples collected in supermarkets in Binghamton, New York; Chicago, IL; Louisville, Kentucky; Atlanta, Georgia; and San Diego, California (Schecter et al. 1996a). For 1995, these authors report that the estimated U.S. mean daily exposure to CDDs/CDFs TEQs for an adult (65 kg body weight) ranges from 34 to 167 pg TEQs. This is equivalent to a daily adult intake of CDDs/CDFs ranging from 0.52 to 2.57 pg TEQs/kg body weight. If PCB TEQs are also considered (where TEF values are available), the daily adult intake ranges from 1.16 to 3.57 pg TEQ/kg body weight/day. A more recent survey of CDDs/CDFs in total diet food samples in Canada was conducted by Ryan et al. (1997). These authors found, through analysis of more than 100 food samples collected from commercial outlets in 1992 and 1993, that the total TEQ intake for CDDs/ CDFs was about 0.8 pg TEQs/kg/day. If all dioxin-like PCBs were also included, this TEQ value rose to approximately 1.2 pg TEQs/kg/day.

In 1995, Schecter and Li (1997) conducted a congener-specific analysis of CDDs, CDFs, and dioxin-like PCBs in US fast foods. These authors reported TEQ values from 0.03–0.28 pg/g wet weight for McDonald's Big Mac, 0.03–0.29 pg/g for Pizza Huts personal pan supreme pizza with all toppings, 0.01–0.49 pg/g for Kentucky Fried Chicken 3 piece original recipe meal, and 0.3–0.31 pg/g for Haagen-Daz chocolate-chocolate chip ice cream. Daily TEQ consumption per kilogram body weight assuming a 65-kg adult, from one serving of each of the fast foods tested ranged between 0.046–1.556 pg/kg. This same value in a 20-kg child (6-year-old) ranged from 0.15 to 5.05 pg/kg. A child on average consumes three times more TEQs on a per kg/body weight basis as compared to adults eating any one of the fast foods tested.

Studies conducted in other industrialized countries have reported similar values to those obtained for the United States. Estimated daily intakes of CDDs and CDFs from various foods were calculated in a Canadian study of foods domestically produced in Canada or imported from the United States (Birmingham et al. 1989). Based on contamination levels (CDDs and CDFs) in samples of meats, eggs, fruits, and vegetables from the United States and Canada, a total daily intake of 1.52 pg TEQs/kg body weight was calculated (for a 60-kg adult). The foods that contributed the most exposure to CDDs/CDFs TEQs were milk, eggs, and beef. Approximately one-half (0.81 pg TEQs/kg) was contributed by milk products. Eggs

and beef were also estimated to make substantial contributions (0.28 and 0.27 pg TEQs/kg, respectively). The total contribution from these animal products to the daily dietary intake is 1.5 pg TEQ/kg body weight (99% of the total). Plant products (fruits, vegetables, and wheat products) contribute only 0.068 pg TEQ/kg body weight/day (1% of the total). The authors also estimated that consumption of freshwater fish was 0.28 pg TEQ/day, thus the total daily intake of CDDs/CDFs amounted to 1.8 pg TEQ/kg body weight (Birmingham et al. 1989).

In a German study where 22 samples of different foodstuffs (cow's milk, butter, pork, beef, lamb, chicken, eggs, and fish) were analyzed for CDDs/CDFs, the total average daily intake of 2,3,7,8-TCDD via food was 0.35 pg/kg/day and for total CDDs/CDFs was 1.3 pg TEQs/kg body weight/day for a 70-kg adult (Beck et al. 1989a). Meat, milk and other dairy products, and fish were the most important food groups contributing 17.9, 26.6, and 38.6 pg TEQ/day, respectively, to the body burden. Eggs, vegetable oil, vegetables, and fruits contributed 3.1, 0.3, 2.4, and 1.3 pg TEQ/day, respectively, to the body burden (Beck et al. 1989a).

In general, vegetation contamination from airborne sources of CDDs results in more substantial exposures to grazing animals due to the proportionally higher accumulation from foliar (leaf) deposition as compared to root uptake (Travis and Hattemer-Frey 1987). OCDD is the CDD contaminant most concentrated by plants. This supports the contention that atmospheric deposition is the primary mechanism by which plants become contaminated, as OCDD is not readily available for root uptake or translocation in plants (Hulster and Marschner 1993; Muller et al. 1993). The concentration of 2,3,7,8-TCDD (due to root uptake and foliar deposition) on vegetation consumed by cows was estimated to be 0.11 ng/kg (97% due to foliar deposition). The estimated total concentration on exposed produce and vegetation consumed by humans was 0.02 ng/kg (67% resulting from foliar deposition) (Travis and Hattemer-Frey 1987). A model has been developed that estimated the CDD content in cow's milk based on emissions from a nearby municipal solid-waste incinerator. The model includes three components that predict atmospheric transport and deposition, soil and grass concentrations, and uptake and bioavailability from fodder to cows. Results indicate that models can be used to estimate CDD contamination in foods (Lorber et al. 1994; Slob and Jaarsveld 1993).

Municipal and industrial incinerators and other combustion sources. Combustion processes are widely recognized as a source of CDDs/CDFs. Using a model, Hattemer-Frey and Travis (1989) estimated a total daily intake of CDD/CDF of 3×10^{-4} ng TEQs/day associated with exposure to a typical,

state-of-the-art municipal solid-waste (MSW) incinerator, assuming a CDD/CDF emission rate based on the geometric mean from 11 proposed MSW facilities. Daily intakes of CDD/CDF in TEQs associated with exposure to a typical state-of-the-art municipal waste incinerator were estimated to be $1.3x10^{-4}$ ng/day from inhalation, $1.1x10^{-4}$ ng/day from total ingestion, $5.7x10^{-5}$ ng/day for mother's milk and $2.2x10^{-6}$ ng/day from dermal absorption. This total daily intake value (3×10^{-4} ng TEQs/day) was 160 times lower than the estimated total daily background intake from all sources of CDDs (0.047 ng/day) to which the general U.S. population is exposed. Thus, the authors concluded that MSW incinerators will not substantially increase human exposure to CDDs/CDFs above normal background levels (Hattemer-Frey and Travis 1989). Table 5-11 shows estimated average daily intakes of CDD/CDF TEQs from various exposure pathways. Fries and Paustenbach (1990) evaluated the effects of 2,3,7,8-TCDD from incinerator emissions to humans. These authors also concluded that airborne emissions of CDDs/CDFs from modern waste incinerators that are equipped with appropriate air pollution devices should not pose a significant health hazard via inhalation of CDD contaminated particles or via contamination of foods regardless of the incinerator location. Hattemer-Frey and Travis (1989) focused on ideal state-of-the-art incinerators. In a more recent analysis, Travis and Hattemer-Frey (1991) estimated that the total daily intake of CDDs/CDFs (TEQs) by a maximally exposed individual living near a modern municipal solid waste incinerator was 0.7 pg/day (0.9% of total daily intake) and 92.8 pg/day (99.1%of total daily intake) was from all other background exposures. These estimates are supported by recent data of Schecter et al. (1995) who found that workers who operate municipal waste incinerators have blood levels of TEQs which do not differ significantly from background levels.

The presence of CDDs in cigarette smoke is also of importance with respect to inhalation exposure since cigarette smoke is inhaled directly into the lungs. Daily exposure to CDDs by smoking 20 cigarettes was estimated to be 18 TEQ pg/day equivalent to a daily intake of 0.26 pg/kg body weight/day (for a 70-kg adult) (Lofroth and Zebuhr 1992).

Consumer products. The presence of CDDs in a variety of consumer products ranging from plastic packaging to colored candle wax, and from textiles to air filters for home-heating systems suggests that CDDs are virtually ubiquitous in the environment (Beck et al. 1989d; Berry et al. 1993; Horstmann and McLachlan 1994; Malisch 1994; Ryan et al. 1992). 2,3,7,8-TCDD and 2,3,7,8-TCDF have been found in many paper products, including coffee-filter paper, although present day paper products now contain less than 1 ng/kg TEQ. Under the preconditions of using 4 small coffee-filter papers (4×1 g) per day containing 5 ppt 2,3,7,8-TCDD and 23 ppt 2,3,7,8-TCDF, which leaches into coffee, a daily exposure of 5 pg

Table 5-11. Estimated Average Daily Intake of TEQs Associated with Exposure to a State-of-the-Art Municipal Waste Incinerator

Exposure pathway	Daily intake (ng/TEQ/day)	Percentage of total intake
Inhalation	1.3×10^{-4}	43
Total ingestion	1.1×10^{-4}	37
Mother's milk	5.7×10^{-5}	19
Dermal absorption	2.2×10^{-6}	1
Total intake	3.0×10^{-4}	100

Source: Hattemer-Frey and Travis 1989

TEQs = toxicity equivalencies of dioxins and dibenzofurans

2,3,7,8-TCDD and 32 pg 2,3,7,8-TCDF or nearly 10 pg TEQs (for these two compounds combined) were calculated for a coffee drinker consuming all the coffee (this is a worst-case assumption that an individual would consume all the coffee brewed) (Beck et al. 1989d). TCDD, PeCDDs, HxCDD, HpCDD, and OCDD were found in all samples derived from consumer products (including plastic packaging, clothes dryer lint, vacuum cleaner dust, room and car air filters, and furnace filter dust), and bleached and unbleached paper products tested. In general, the more highly chlorinated congener groups (HxCDD, HpCDD and OCDD) exhibited the highest concentrations. The highest levels of most congeners were found in home-furnace filter dust, which contained HxCDD, HpCDD and OCDD at concentrations up to 135 ppt, 9,990 ppt, and 24,600 ppt, respectively (Berry et al. 1993). Car air filters displayed a different CDD profile than the other products with the highest concentration detected for TCDD (2,080 ppt), PeCDD (1,320 ppt) and HxCDD (1,320 ppt). TEQ values for CDD/CDF were highest for the home furnace filter (170 ppt), car air filter (84 ppt), and room air filter (29 ppt).

Adipose tissue residues. The general population of the United States is continuously exposed to small amounts of CDDs, as exemplified by the fact that all human adipose tissue samples contain CDDs (Orban et al. 1994; Patterson et al. 1986a; Ryan et al. 1986; Schecter et al. 1986b; Stanley 1986; Stanley et al. 1986). Results of the National Human Adipose Tissue Survey (NHATS) conducted in 1982, which estimated the general population exposure to toxic organic chemicals, showed that 2,3,7,8-TCDD was detected in 35 of 46 (76%) composite samples with an average lipid-adjusted concentration of 6.2±3.3 ppt (Stanley 1986; Stanley et al. 1986). The average concentration of the other CDD compounds ranged from 43.5 ppt for PeCDD (detected in 91% of the composites) to 694 ppt for OCDD (detected in 100% of the composites). The congener distributions found in adipose tissue are similar to those found in human milk (i.e., OCDD was the most abundant and 2,3,7,8-TCDD the least abundant congener). The analysis of 46 composite adipose samples verified the prevalence of the 2,3,7,8-substituted tetra- through octa CDDs in the U.S. population (Stanley 1986; Stanley et al. 1986). The number of adipose samples in each composite was defined based on differences in age, gender, race, and regional affiliation of the individuals from whom the specimens were collected. The results also suggested that adipose tissue concentrations tended to increase with age for the congeners tested, with the exception of PeCDD. The NHATS study also showed regional differences in CDD concentrations in adipose tissue, with the greatest exposure occurring in the East North Central region of the United States (i.e., Ohio, Michigan, Indiana, Illinois, and Wisconsin). Exposure was also relatively high in the mid-Atlantic and East South Central regions (Phillips and Birchard 1991).

Results of the more recent 1987 NHATS Study were summarized by Orban et al. (1994). Human adipose samples from autopsy cases were obtained through a network of pathologists to provide a representative sample of the general U.S. population. NHATS samples collected during 1987 were analyzed for 7 CDDs and 10 CDFs and the results are summarized in Table 5-12. Data were evaluated by census region, age group, sex, and racial group. The average concentration of 2,3,7,8-TCDD in adipose tissue in the U.S. population was estimated to be 5.38 pg/g (±6%). The 1987 survey data clearly show that nearly all of the CDD/CDF congeners increased with the age of the donor (i.e., the highest concentrations occur in the 45+ age group and the lowest concentrations occur in the 0–14 age group). On a regional basis, only the average concentration of 2,3,4,7,8-PeCDF was statistically different in the Northeast (13.7 pg/g) compared to the national average (9.7 pg/g). Orban et al. (1994) also compared NHATS 1987 data to the NHATS 1982 data. Because of slight differences in study design, the congeners that were most comparable between the two surveys were 2,3,7,8-TCDD and 2,3,7,8,-OCDD. Statistical analysis of the two survey data sets revealed no significant differences between the national average concentration of 2,3,7,8, TCDD determined in 1982 and 1987. There were also no significant differences in the profiles with respect to census region, sex, and race. With respect to age, however, there was a significant difference; the 1987 NHATS data demonstrated that the concentration of 2,3,7,8-TCDD consistently increased with the age of the donor. The average concentration of 2,3,7,8-TCDD in the 1987 survey increased from 1.98 pg/g in the 0–14-year-old group, to 4.37 pg/g in the 15–44-year-old group, to 9.4 pg/g in the 45+-year-old group. The average concentration of OCDD in the 1982 survey was 768 pg/g (±79.7 standard error) as compared to 724 pg/g (± standard error 28.6) in the 1987 study.

Analysis of human adipose tissue from 35 autopsy cases from Georgia and Utah found 2,3,7,8-TCDD in all of the samples at a concentration range (whole-weight) of 2.7–19 ppt (Patterson et al. 1986b). The geometric mean value for 2,3,7,8-TCDD in these samples on a whole-weight basis was 7.1 ppt. The geometric mean value for 2,3,7,8-TCDD in 31 of these samples on a lipid basis was 9.6 ppt. The histories of exposure to 2,3,7,8-TCDD were not known for any of the autopsy cases (Patterson et al. 1986b).

Blood residues. CDDs/CDFs were measured in the blood (lipid basis) of 10 individuals in Germany with no prior CDD exposure (Päpke et al. 1989b). OCDD was the most abundant congener present (mean 610.8 ppt; range 439–889 ppt), followed by 1,2,3,4,6,7,8-HpCDD (mean 88.2 ppt; range 30-142 ppt), HxCDD (mean 75.7 ppt; range 52–99.8 ppt), 1,2,3,7,8-PeCDD (mean 16.5 ppt; range 5.6–39 ppt), and 2,3,7,8-TCDD (mean 4 ppt; range <1.5–9.1 ppt). Mean blood levels of CDFs ranged from 24 to 46.3 ppt. Detection limits for 2,3,7,8-TCDD were 1–4 ppt (extractable lipids) which corresponds to 0.005–0.02 ppt

Table 5-12. Dioxins and Dibenzofurans in Adipose Tissue of the General U.S. Population[a]

	Concentration (pg/g, lipid basis)[b]		
Compound	Minimum	Median	Maximum
2,3,7,8-TCDD	<0.980[b]	6.54	15.1
2,3,7,8-TCDF	0.893	1.89	3.88
1,2,3,7,8-PeCDD	<2.44	10.2	24.4
1,2,3,7,8-PeCDF	<0.066[c]	0.249	1.42
2,3,4,7,8-PeCDF	<0.264[c]	9.21	29.2
1,2,3,7,8,9-HxCDD	<3.86[c]	11.5	22.0
1,2,3,7,8,9-HxCDF	<0.290[c]	0.341	1.98
1,2,3,4,7,8/1,2,3,6,7,8-HxCDD	13.3	76.1	174.00
1,2,3,4,7,8-HxCDF	<3.11[c]	7.30	17.0
1,2,3,6,7,8-HxCDF	<0.556[c]	5.03	14.3
2,3,4,6,7,8-HxCDF	<0.377[c]	0.479	2.49
1,2,3,4,6,7,8-HpCDD	20.9	11.00	230.0
1,2,3,4,6,7,8-HpCDF	<1.15[c]	17.7	32.5
1,2,3,4,7,8,9-HpCDF	0.731[c]	0.715	1.74
OCDD	152.0	838.0	1630.0
OCDF	<0.680[c]	1.19	13.2

[a] Values represent analysis of 48 composite samples collected from 865 individuals in the general population.
[b] Not detected concentrations were replaced by one-half the limit of detection.
[c] The minimum concentration is less than the minimum reported limit of detection.

HpCDD = heptachlorodibenzo-*p*-dioxin; HpCDF = heptachlorodibenzofuran; HxCDD = hexachlorodibenzo-*p*-dioxin; HxCDF = hexachlorodibenzofuran; OCDD = octachlorodibenzo-*p*-dioxin; OCDF = octachlorodibenzofuran; PeCDD = pentachlorodibenzo-*p*-dioxin; PeCDF = pentachlorodibenzofuran; TCDD = tetrachlorodibenzo-*p*-dioxin; TCDF = tetrachlorodibenzofuran

Source: Orban et al. 1994

for whole blood with a lipid content of 0.5% (Päpke et al. 1989b). These authors reported that blood levels of CDDs/CDFs from persons with no known exposure to CDDs corresponded to those levels measured in adipose tissue of unexposed individuals. Needham et al. (1996) reported reference range data for CDDs and CDFs in blood of individuals who presumably had not been exposed occupationally to these compounds. The range of means in ppt (lipid basis) in blood for 7 CDDs, 11 CDFs, and 4 PCBs are summarized in Table 5-13. OCDD was the most abundant congener present (range of means 560–1,000 ppt), followed by 1,2,3,4,6,7,8-HpCDD (range of means, 80.3–230 ppt), 1,2,3,6,7,8-HxCDD (range of means, 45–85 ppt), 1,2,3,7,8-PeCDD (range of means, 6.6–32 ppt), and 2,3,7,8-TCDD (range of means, 3.2–10.1 ppt). Mean blood levels of CDFs ranged from not detected to 27 ppt. The TEQ range in mean blood levels was 13.7–41.39 ppt for all CDDs and 15.1–58.0 ppt for CDDs/CDFs.

Tepper et al. (1997) compared serum levels of CDD and CDF concentrations in 16 community residents who had no occupational exposure to these compounds. OCDD was the most abundant congener present (range, 285–1,489 ppt), followed by 1,2,3,4,6,7,8-HpCDD (range, 64.1–115 ppt), 1,2,3,6,7,8-HxCDD (range, 48.3–101 ppt), 1,2,3,7,8-PeCDD (range, 2–7.8 ppt), and 2,3,7,8-TCDD (range, 1.5–3.5 ppt). Mean blood levels of CDFs ranged from 0.8 to 31.3 ppt. The mean in TEQs was 13.5 ppt (range, 9.5–19.1) for all CDDs, 5.0 ppt (range, 3.4–8.8 ppt) for all CDFs, and 19.1 ppt (range, 12.9–25.9 ppt) for CDD/CDFs.

Most recently, Michalek et al. (1998) measured levels of 2,3,7,8-TCDD in 1,302 unexposed Air Force Vietnam-era veterans. These veterans served as controls in the 20-year epidemiologic study of Air Force veterans of Operation Ranch Hand, the unit responsible for aerial spraying of Agent Orange in Vietnam. These authors reported mean 2,3,7,8-TCDD concentrations in blood of 4.32±2.53 ppt for the control group. The 99th percentile of the distribution was less than or equal to 10.4 ppt.

Needham et al. (1991) also showed that human adipose tissue concentrations of CDDs may be correlated with blood serum levels after adjusting for total lipid content. On a lipid basis, total CDD/CDFs are higher in blood than adipose tissue. Partitioning is not identical in these tissues; 2,3,7,8-TCDD levels are almost identical in blood and adipose tissues, but OCDD levels are higher in blood. However, the presence of OCDD at levels of 5,000–10,000 pg/person when concentrations in food are generally in the low pg/g level suggests that the contribution of food to the OCDD body burden in humans requires further study (Rappe 1993).

Table 5-13. Reference Range Levels and TEQs of CDDs, CDFs, and Coplanar PCBs in Whole Blood (Lipid Basis) for the General Population

	Compound	Range of means (ppt)	Reference range (ppt)	TEQ (ppt)
CDDs	2,3,7,8-TCDD	3.2–10.1	ND–38	3.2–10.1
	1,2,3,7,8-PeCDD	6.6–32	ND–180	3.3–16
	1,2,3,4,7,8-HxCDD	6.3–13	3.1–58	0.63–1.3
	1,2,3,6,7,8-HxCDD	45–85	17–494	4.5–8.5
	1,2,3,7,8,9-HxCDD	7.1–21.9	3.5–51	0.71–2.19
	1,2,3,4,6,7,8-HpCDD	80.3–230	ND–1260	0.8–2.3
	OCDD	560–1,000	64–2,550	0.56–1
CDD Total TEQ[a]		13.7–41.4		
CDFs	2,3,7,8-TCDF	1.1–9	ND–32	0.11–0.9
	1,2,3,7,8-PeCDF	ND	ND	–
	2,3,4,7,8-PeCDF	5–27	ND–77	0.25–13.5
	1,2,3,4,7,8-HxCDF	4.5–11	1.7–28	0.45–1.1
	1,2,3,6,7,8-HxCDF	4.5–8.5	1.8–18	0.45–8.5
	1,2,3,7,8,9-HxCDF	ND	ND	–
	2,3,4,6,7,8-HxCDF	ND	ND	–
	1,2,3,4,6,7,8-HpCDF	8.7–22.8	ND–55	0.087–0.23
	1,2,3,4,7,8,9-HpCDF	ND	ND	–
	OCDF	ND	ND	–
CDF Total TEQ		1.4–16.6[a]		
PCBs	3,3',4,4'-TCB	11.7	ND–27.9	0.00585
	3,4,4',5-TCB	10.5	1.5–21.3	0
	3,3',4,4',5-PCB	135	14.6–371	13.5
	3,3',4,4',5,5'-HxCB	69	29.5–174	0.69
PCB Total TEQ		14.2[b]		

[a] TEQ values calculated by multiplying range of means values by EPA toxic equivalency value.
[b] TEQ calculated by multiplying range of means value by 0.0005, 0, 0.1, and 0.01 for 3,3',4,4'-TCB, 3,4,4',5-TCB, 3,3',4,4',5-PCB, 3,3',4,4',5,5'-HxCB, respectively.

CDDs = chlorinated dibenzo-*p*-dioxins; CDFs = chlorinated dibenzofurons; HpCDD = heptachlorodibenzo-*p*-dioxin; HpCDF = heptachlorodibenzofuran; HxCB = hexachlorobiphenyl; HxCDD = hexachlorodibenzo-*p*-dioxin; HxCDF = hexachlorodibenzofuran; ND = not detected; OCDD = octachlorodibenzo-*p*-dioxin; OCDF = octachlorodibenzofuran; PCB = polychlorinated biphenyl; PeCDD = pentachlorodibenzo-*p*-dioxin; PeCDF = pentachlorodibenzofuran; TCB = tetrachlorobiphenyl; TCDD = tetrachlorodibenzo-*p*-dioxin; TCDF = tetrachlorodibenzofuran; TEQ=Toxicity equivalency concentration.

Source: Needham et al. 1996

5.5.2 Occupational Exposure

Occupational exposure to CDDs occurs primarily through inhalation and dermal contact of fire fighters and cleanup workers involved with transformers containing PCBs and polychlorobenzenes; in workers involved in incineration operations; in workers in metal reclamation facilities, and in workers producing and handling pesticides, hexachlorophene, trichlorophenol, or other chlorinated compounds (e.g., pentachlorophenol) that may contain small impurities of 2,3,7,8-TCDD or other CDDs (Päpke et al. 1992). In addition, these authors reported that the CDD/CDF homologue profiles in whole blood of workers engaged in a variety of different chemical processes or in occupational accidents exhibited distinct CDD/CDF patterns (Päpke et al. 1992).

A dust sample collected from the ambient atmosphere of a municipal incineration plant in Europe over a 6-day period was analyzed for CDDs. The concentrations of 2,3,7,8-substituted congeners ranged from 0.9 ppb (2,3,7,8-TCDD) to 310 ppb (1,2,3,4,6,7,8-HpCDD) (Tong et al. 1989a). These results indicate that the ambient atmosphere of a municipal incinerator can be contaminated by CDDs by means of fly ash and possibly other incineration products; thus, municipal incinerator workers are at risk of exposure to CDDs (Tong et al. 1989a). Blood analysis of 10 workers at a municipal solid-waste incinerator in Germany showed elevated CDD levels of 4 workers whose work was associated with exposure to fly ash and slag (Päpke et al. 1993). In several individuals studied, the higher chlorinated CDDs/CDFs especially the 2,3,7,8-substituted HxCDD, HpCDD, and OCDD congeners showed slightly elevated levels.

Compared with background 2,3,7,8-TCDD levels (3.6 ppt), workers involved in trichlorophenol production had elevated 2,3,7,8-TCDD blood levels, with a mean concentration of 332 ppt (Päpke et al. 1992). PCP manufacturing resulted in the greatest increases for workers with respect to all congeners, with OCDD blood levels of approximately 300,000 ppt. PeCDF, HxCDF, and HpCDF levels in the blood were elevated in workers at a metals reclamation plant (Päpke et al. 1992). Workers exposed to CDD as a result of an industrial accident had mean 2,3,7,8-TCDD blood levels of 53 ppt almost 36 years after the incident (Päpke et al. 1992). In one documented case, a U.S. domestic agricultural worker was exposed to 2,3,7,8-TCDD during spraying of 2,4,5-T herbicide on pasture land and hay ground. A sample of the herbicide that he used contained 7.7 ppb 2,3,7,8-TCDD. 2,3,7,8-TCDD levels measured in the worker's adipose tissue 5 years post-exposure were 72 ppt (whole weight) or 77 ppt (lipid basis) (Tong et al. 1989b). Thirty-two years after an industrial accident in a chemical plant manufacturing trichlorophenol, the average lipid-adjusted concentration of 2,3,7,8-TCDD in the adipose tissue of exposed workers who

developed symptoms (chloracne and other illnesses) was 49 ppt (range of 11-141 ppt) (Schecter and Ryan 1988).

In a recent study by Tepper et al. (1997), serum levels of CDDs and CDFs were measured in pulp and paper mill workers in the United States. These authors reported that serum levels of CDDs and CDFs among 46 long-term workers at a pulp and paper mill were not appreciably different among three exposure groups studied (community residents, low-exposure-potential worker group, and high-exposure-potential worker group). Serum CDD TEQs were 13.5 ppt (range, 9.5–19.1 ppt), 15.9 ppt (range, 6.5–31.8 ppt), and 13.3 ppt (range, 7.5–24.9 ppt) respectively. Total TEQ for both CDDs and CDFs were similar for the three groups at 19.1 ppt, 21.2 ppt and 18.1 ppt, respectively. Serum levels of CDDs and CDFs in this study were within the range previously reported for persons with no known occupational exposure.

A series of adipose tissue samples collected from one exposed individual, as well as surgical and autopsy specimens from four control individuals, was analyzed for CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) (Schecter et al. 1985a). All specimens were obtained from persons residing in urban or rural areas of upstate New York during 1983 or 1984. The worker who had been exposed to soot containing PCBs, CDFs, and small amounts of CDDS from the CDD/ CDF-contaminated Binghamton State Office Building in New York, had a total CDD concentration (whole-weight basis) of 1,015 ppt, whereas the average total CDD concentration for the controls was 765 ppt. Mean concentrations were highest for OCDD among all the CDD congener groups in both the controls (585 ppt) and the exposed person (690 ppt). 2,3,7,8-TCDD concentrations were lowest in both groups, an average of 6.3 ppt for the controls and 11.6 ppt for the exposed person. Intermediate levels were found for PeCDD (7.5–13.8 ppt), HxCDD (6.8–64.2 ppt), and HpCDD (2.6–119 ppt) in the control groups. Intermediate levels were also found in the exposed individual for PeCDD (15 ppt), HxCDD (7.3–72.6), and HpCDD (9.6–209 ppt) (Schecter et al. 1985a).

An occupational study of workers exposed to CDDs at a Missouri chemical plant from 1968 to 1972 found a mean 2,3,7,8-TCDD concentration of 390 ppt in the adipose tissue of 4 exposed workers measured 13–17 years post-exposure. The chemical plant made 2,4,5-trichlorophenol (2,4,5-TCP), which was used as a feedstock to produce butyl esters of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T esters) and hexachlorophene between 1968 and 1972. The 2,3,7,8-TCDD was generated as an unintended contaminant during the production of 2,4,5-TCP. Consequently, workers involved in these processes were potentially exposed to 2,3,7,8-TCDD. The mean concentration of 2,3,7,8-TCDD found in these workers was 45 times higher than the mean of 8.7 ppt reported for 7 unexposed Missouri residents (Patterson et al. 1989a).

Another group that is occupationally exposed to CDDs includes analytical chemists involved in the synthesis of CDDs for research purposes or those involved in analysis of environmental samples contaminated with CDDs. Schecter et al. (1994b) reported that a chemist who had been involved in synthesizing 2,3,7,8-TCDD in 1956 at a university research laboratory had subsequently developed chloracne, headaches, backaches, and severe leg pains when he walked. During 1990–91, approximately 35 years after the chemist's initial exposure, blood CDDs analysis was performed to determine whether residual CDD levels still remained. Schecter et al. (1994b) reported that blood TCDD levels (on a blood-lipid basis) were 20 ppt as compared to 3–5 ppt measured in a control population of 100 individuals. Analytical laboratory personnel who are involved in analyzing CDD-contaminated samples also may be exposed to higher levels of CDD contamination than the general population (Hesso et al. 1992; Oliver 1975).

In a study conducted by NIOSH, serum levels of 2,3,7,8-TCDD were measured in 27 U.S. chemical workers previously exposed to CDDs-contaminated products (Fingerhut et al. 1989). The workers were employed at two U.S. facilities that produced 2,4,5-TCP and 2,4,5-T between 1951 and 1972. Serum levels of 2,3,7,8-TCDD were also measured in 19 unexposed controls. A mean serum 2,3,7,8-TCDD level of 208.2 ppt found in the exposed workers exceeded (by more than 25 times) the mean background level of 8.2 ppt found in the controls who did not produce these chemicals (Fingerhut et al. 1989).

Workers who are involved with incineration operations may be exposed to levels of CDDs that are higher than background levels to which the general population is exposed. Schecter et al. (1991b) measured CDD and CDF blood levels on a lipid basis in pooled blood samples from a group of 56 New York City incinerator workers and 14 controls. The levels of 11 of the 18 CDD/CDF congeners measured were increased in the incinerator workers as compared to the controls. CDD levels in incinerator workers were 48, 17, 27, 30, and 31% higher for 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD, respectively. Only 2,3,7,8-TCDD and 1,2,3,4,7,8-HxCDD were lower in incinerator workers' blood than in controls (5 and 15% lower, respectively). Overall, the total CDD/CDF level in workers' blood was, 1,007.2 ppt (lipid basis) as compared to 747.3 ppt for the controls (Schecter et al. 1991b). In the past, workers involved in the production or use of hexachlorophene, trichlorophenol, 2,4,5-T, and other compounds that are no longer used were also exposed to 2,3,7,8-TCDD. Workers in pulp and paper mills also have the potential for 2,3,7,8-TCDD exposure because of the occurrence of 2,3,7,8-TCDD in bleached kraft paper-making processes (Clement et al. 1989; Kuehl et al. 1987a; Tepper et al. 1997); although exposure to this source has probably declined since

1990 with the implementation of bleach plant modifications at many pulp and paper mills (NCASI 1993). Workers in the sawmill industry who handle treated lumber may be exposed to chlorophenols, particularly PCP; consequently, they may be exposed to higher levels of the more highly chlorinated CDDs (Kalliokoski and Kauppinen 1990). Workers employed at sites of improper chemical waste disposal (trichlorophenol, hexachlorophene, 2,4,5-T) have a greater potential for exposure to 2,3,7,8-TCDD via inhalation or via oral or dermal contact than the general population.

A current estimate of the number of workers in the United States that are potentially exposed to CDDs is not available. At-risk worker populations include incinerator personnel, those involved in production or use of chlorinated compounds containing CDD contamination (e.g., hexachlorophene, PCP, 2,4,5-trichlorophenol, and 2,4-D), analytical research chemists, and workers at chemical waste disposal sites, electrical utility workers, and firefighters.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, Children's Susceptibility.

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

Children are primarily exposed to CDDs in the same manner as adults in the general population (i.e., via consumption of foods contaminated with small amounts of CDDs, particularly meat, milk and other dairy products, and fish). Children that are at additional risk of exposure primarily through dietary habits, include: infants and young children who are breast-fed; children of recreational and subsistence fishers, who typically consume larger amounts of locally caught fish and shellfish than the general population;

children of subsistence hunters, particularly those in the high latitudes, who typically consume large amounts of locally caught game especially marine mammals; and children of subsistence farmers living in areas contaminated with CDDs (either by waste incinerators or the use of CDD- contaminated sewage on their land) who exclusively consume their own farm-raised beef and dairy products (see Section 5.7).

The human fetus is exposed to CDDs/CDFs through transplacental transfer from the mother. Schecter et al. (1990a) reported 2,3,7,8-TCDD concentrations in liver tissue of three still-born infants ranging from 0.03 to 0.18 ppt (whole weight basis) and 1.3 to 4.3 ppt (lipid weight basis). Schecter et al. (1990a) also reported CDD/CDF concentrations in liver tissue of three stillborn infants ranging from 2.1 to 4.92 ppt (whole weight basis) and 98 to 104 ppt (lipid weight basis). The TEQ for CDD/CDFs combined ranged from 0.14 to 0.49 ppt (whole weight basis) and 6.4 to 12 ppt (lipid weight basis). In a more recent study, Schecter et al. (1996e) reported TEQs for CDDs/CDFs in placental material ranging from 8.4 to 17.6 ppt (lipid basis). In a pooled sample of fetal tissue (8–14 weeks), the TEQ was 5.3 ppt (lipid basis). Concentrations of 2,3,7,8-TCDD in adipose tissue and liver were also reported by Kreutzer et al. (1997) for stillborns at levels between 0.2 and 0.8 ppt and 0.3 to 0.7 ppt, respectively. Kreutzer et al. (1997) developed a pharmacokinetic model for 2,3,7,8-TCDD that predicted a decrease in body burdens during the first year for non-breast-fed infants and this was supported by empirical data (see Section 2.3.4.4, Transfer of CDDs Through the Placenta and Breast Milk).

In addition to transplacental transfer, CDDs and CDFs have been found in human milk (Fürst et al. 1992; Ryan et al. 1993a; Schecter and Gasiewicz 1987b; Schecter et al. 1986a, 1989d, 1989e, 1989g, 1991a); human milk is thus a potential source of CDDs for nursing infants and children (see Section 5.5). In Binghamton, New York, and Los Angeles, California, human breast milk was found to contain almost identical levels of detectable CDDs on a lipid basis probably because food consumption and sources are similar across the United States (Schecter et al. 1989e). Mean values of two pooled samples (n=42) from both cities showed that OCDD was the most abundant congener present (233 ppt), followed in decreasing order by total HxCDD (42.65 ppt), 1,2,3,4,6,7,8-HpCDD (42 ppt), 1,2,3,6,7,8-HxCDD (30.5 ppt), 1,2,3,7,8-PeCDD (6.7 ppt), 1,2,3,7,8,9-HxCDD (6.2 ppt), 1,2,3,4,7,8-HxCDD (4.95 ppt), and 2,3,7,8-TCDD (3.3 ppt). The total CDDs value was reported as 327 ppt. The TEQ for CDDs/CDFs, but not PCBs in breast milk in the United States was 17 ppt (Schecter et al. 1989e). Between 1986 and 1987, concentrations of CDDs found in breast milk sampled from Canadian women ranged from 2.2 ng/kg (ppt) (lipid basis) for TCDDs to 173 ppt for OCDD. In addition, the combined CDD/CDF mean TEQ of 15.6 ppt (lipid basis) declined from a TEQ of 24.7 ppt measured in 1981–1982 (Ryan et al. 1993a).

CDD/CDF concentrations also have been measured in breast milk in several foreign studies. Concentrations of CDDs/CDFs were also measured in preserved breast milk from 505 persons (both primiparas and multiparas) in Japan from 1978 to 1984 (Ogaki et al. 1987). OCDD was a major component in primiparas' milk (789 ppt) and multiparas' milk (518 ppt) (Ogaki et al. 1987). For the primiparas, average concentrations found for HpCDD, HxCDD, PeCDD, total TCDD, and 2,3,7,8-TCDD were 150, 76, 15, 37, and 13 ppt, respectively. The average CDD concentrations found in the milk of multiparas were generally lower than the average concentrations found in the milk of primiparas. For the multiparas, average concentrations for HpCDD, HxCDD, PeCDD, and TCDD (not 2,3,7,8) were 75, 56, 11, and 19 ppt, respectively (Ogaki et al. 1987). A similar study in Germany between 1984 and 1991 found mothers nursing their second child had 20% less CDD TEQs in their milk than did primigravidae (Fürst et al. 1992). CDD concentrations in human milk can be directly correlated with the age of the mother and the amount of animal (but not vegetable) fat and protein consumed, suggesting that meat, milk and other dairy products, and fish are the major sources of CDD intake (Pluim et al. 1993a). The fact the CDD concentrations in milk fat were significantly related to age is in agreement with the results of Stanley et al. (1986) and Orban et al. (1994) who reported a strong correlation between age group and CDD levels in adipose tissue in the general U.S. population. The positive correlation can be expected because of the long half-life of CDDs in humans (7–11.3 years) (Pirke et al. 1989; Wolfe et al. 1994).

Estimated daily intakes of CDD/CDF TEQs by nursing infants in the United States have been reported by Schecter and Gasiewicz (1987a). The daily intake by nursing infants in the United States was estimated to be 83.1 pg TEQs/kg body weight/day. To determine this daily intake, various assumptions were made regarding infant body weight (10 kg), duration of nursing, average amount of milk consumed, and gastrointestinal absorption. It was also assumed that breast milk was the only source of CDDs while the infant was nursing during the first year of life. From results of earlier studies that determined the concentrations of CDDs/CDFs in human breast milk in the United States (Schecter et al. 1989e) and in cow’s milk and soybean-derived infant formula sold in the United States (Schecter el al. 1989c) (see Section 5.4.4), Schecter et al. (1994e) estimated slightly lower intakes of 35–53 pg TEQ/kg of body weight/day for infants (7.3 kg) that were breast-fed within the first year of life as compared to 0.07–0.16 pg TEQ/kg of body weight for infants who were fed soy formula.

Exposure of infants and young children to CDDs may be very high because of their relatively high consumption of milk, including breast milk (ECETOC 1992). Schecter et al. (1994e) evaluated the intake of CDDs/CDFs from human breast milk and estimated that high levels reported for breast milk in the

United States (. 17 ppt TEQ on a lipid basis) contribute 35–53 pg TEQ/kg of body weight per day to the nursing infant in its first year of life (Schecter et al. 1989e). The CDD concentrations in cow's milk and soy-based formula were much lower than in breast milk (327 ppt) (Schecter et al. 1991a). The following concentrations for CDDs (on a lipid basis) were reported: cow's milk (25.1 ppt), 2% cow's milk (32.3 ppt), Similact™ infant formula (39 ppt), Isomil™ infant formula (23.3 ppt), and Prosobee™ infant formula (42.7 ppt) (Schecter et al. 1989c). The TEQ values for cow's milk and soy-based infant formula were also much lower than for human breast milk (. 17 ppt). The corresponding TEQ values for CDDs/CDFs (on a lipid basis) were reported: cow's milk (2.1 ppt), 2% lowfat cow's milk (0.79 ppt), Similac™ infant formula (0.08 ppt), Isomil™ infant formula (0.05 ppt), and Prosobee™ infant formula (0.127 ppt) (Schecter et al. 1989c). Schecter and Gasiewicz (1987a, 1987b) calculated TEQ values for CDDs/CDFs in human milk in two populations in Vietnam and in the general population in the United States. These authors reported mean values during the 1980s of 1.04 pg TEQ/g (whole milk basis) for the United States (maximum 4.72 pg TEQ/g), a mean of 1.11 pg TEQ/g for South Vietnamese (maximum value 4.38 pg TEQ/g) exposed to Agent Orange sprayed between 1962 and 1970, and a mean of 0.065 pg TEQ/g (maximum value 0.18 pg TEQ/g) for a North Vietnamese population that was not exposed to Agent Orange. These authors concluded that some infants in the United States (whose mothers had CDD milk concentrations in the upper range of measured values) were being exposed to mean concentrations comparable to levels observed in the South Vietnamese population exposed to Agent Orange (Schecter and Gasiewicz 1987a, 1987b).

The highest exposure to CDD-contaminated breast milk reported was associated with the widespread use of Agent Orange as a defoliant during the Vietnam War. Human milk specimens from Ho Chi Minh City and Song Be Province in South Vietnam had lower 2,3,7,8-TCDD values in the late 1980s (7.1 and 17 ppt lipid basis) (TEQ values of 18.5 and 31.7 ppt), respectively, than they did in the 1970s when Agent Orange spraying occurred (Schecter et al. 1989e). A 1970 mean value for 2,3,7,8-TCDD in human milk in South Vietnam was reported to be 484.9 ppt (range, not detectable to 1,450 ppt) (Baughman and Meselson 1973; Schecter et al. 1986a). These values serve as reference values for the highest levels of 2,3,7,8-TCDD documented in human milk (Schecter et al. 1989e). Estimated daily intakes of TEQs by nursing infants from Vietnam have been reported (Schecter and Gasiewicz 1987a). The estimated daily intake by nursing infants in southern Vietnam in 1970 was 908 pg TEQs/kg body weight/day, whereas the daily intakes in southern and northern Vietnam in 1984 were 88.7 and 5.1 pg TEQs/kg body weight/day, respectively. Analysis of 9 milk samples from individuals living in northern Vietnam showed no detectable concentrations of 2,3,7,8-TCDD (detection limit 2 ppt) (Schecter and Gasiewicz 1987a). To determine

these daily intakes, various assumptions were made regarding infant weight, duration of nursing, average amount of milk consumed, and gastrointestinal absorption. It was also assumed that breast milk was the only lifetime source of exposure to CDDs during the first year of life. In another study, Tarkowski and Yrjanheikki (1989) evaluated the health risks associated with human milk. These authors concluded that levels of CDD/CDFs in breast milk did not present a health risk to infants and children and that there was no justification for limiting breast-feeding. However, these authors believed there was a need for primary prevention of CDD/CDF exposure in humans. Because of the relatively short period of intake and the accepted benefits of breast-feeding, the World Health Organization did not recommend limitations on breast-feeding at the levels of background exposures to CDDs and CDFs (WHO 1991). More recently, Pohl and Hibbs (1996) reviewed recent studies indicative of a possible link between development of subtle health effects in children and their exposure to CDDs and CDFs from maternal milk. It is the ATSDR position that for background exposures, the benefits of breast feeding outweigh any potential risk associated with exposure. For higher CDDs levels in breast milk, the safety of breast-feeding may be of concern in some cases.

Two recent studies have looked at ways to reduce CDD exposure in breast-fed infants. Koppe (1995) reported that exposure before and after birth to CDDs and PCBs has given rise to subtle abnormalities (disturbed cognitive development and delayed motor development) in approximately 10% of newborns in the Netherlands. This author examined possibilities of reducing this exposure by influencing the diet of the lactating mother. Mobilization of fatty acids from adipose tissue will cause release of stored CDDs which will then be secreted in breast milk. Two maternal diets were tested for their ability to reduce concentrations of CDDs in human milk. One diet was a low fat/high carbohydrate/low CDD diet, while the second was a high fat/low carbohydrate/low CDD diet. Despite significant changes in fatty acid profiles of the milk, no significant changes in CDD concentrations in breast milk were observed. The author concluded that short-term dietary measures will not reduce CDDs in breast milk. A lowering of CDD intake must occur years before the woman becomes pregnant. An important food source for the women is cow's milk and other dairy products and these are responsible for about half of the daily exposure CDDs and PCBs in women in the Netherlands, so levels of the compounds in dairy foods must be lowered. In addition, the author believes that a lowering of CDD concentrations in fish is also necessary. Based on the results of his dietary study, Koppe (1995) reported that daily dietary intake of CDDs during lactation represents only 14% of the daily secretion of CDD in breast milk, while 86% was derived from CDDs stored in adipose tissue. Thus, reducing dietary intake of CDDs during lactation would only reduce CDDs in milk by 14%. Schlaud et al. (1995) also reported that to reduce organochlorine residue levels including

CDDs in human breast milk in the short-term, nursing mothers should be advised not to try to reduce their body weight until after lactation. These authors reported statistically significant positive associations between breast milk contamination and average dietary fat intake per week (P=0.001) and proximity of residence to hazardous waste sites (P<0.05) for CDDs. These authors believe that public promotion of a lower dietary fat intake may reduce the lifetime accumulation of CDDs in human fatty tissues and in the long-term, resulting in lower concentrations in breast milk as well.

In addition to exposure to CDDs through consumption of breast milk, cow's milk, and soy-based infant formula, older children can be exposed through dietary practices similar to those of adults in the general population (see Section 5.4.4). One study has looked at the exposure that might occur in a 6-year-old child who consumes "fast foods." In 1995, Schecter and Li (1997) conducted a congener-specific analysis of CDDs, CDFs, and dioxin-like PCBs in U.S. fast foods. These authors reported a CDD/CDF TEQ value, depending on the treatment of not detected congeners, from 0.03–0.28 pg/g wet weight for one McDonald's Big Mac, 0.03–0.29 pg/g for one Pizza Hut personal pan pizza supreme with all toppings, 0.01–0.49 pg/g for one Kentucky Fried Chicken 3-piece original recipe meal, and 0.3–0.31 pg/g for one Haagen-Daz chocolate-chocolate chip ice cream. The daily intake from one serving of each of the fast foods tested, assuming a 20-kg child (6 years old), ranged between 0.15 and 5.05 pg TEQ/kg body weight. These authors calculated that, on average, a child (6 years old) consumes 3 times more TEQs on a per kg/body weight basis than an adult eating any one of the fast foods tested.

As a result of the transfer of CDDs through the placenta to the fetus, by breast milk to infants and young children, and by lifelong dietary intakes from the consumption of meat, milk and dairy products, and fish, CDDs are found to be widespread in the adipose tissue of members of the general population (Orban et al. 1994). Human adipose samples from the recent 1987 NHATS Study provide a representative sample of CDD body burden in the general U.S. population (see Section 5.5.1). The average concentration of 2,3,7,8-TCDD in the U.S. population was estimated to be 5.38 pg/g (±6%). The 1987 survey data clearly show, however, that nearly all of the CDD/CDF congeners in adipose tissue increased with the age of the donor (i.e., the highest concentrations occur in the 45+ age group and the lowest concentrations occur in children in the 0–14 age group). The average concentration of 2,3,7,8-TCDD in the 1987 survey increased from 1.98 pg/g in the 0–14-year-old group, to 4.37 pg/g in the 15–44-year-old group, to 9.4 pg/g in the 45+-year-old group.

Children may be exposed to CDDs through a variety of lifestyle practices of their parents or of their own. For example, CDD/CDF concentrations have been reported in cigarette smoke (Lofroth and Zebuhr 1992; Muto and Takizawa 1989) (see Section 5.4.4). Young children and infants may be exposure to CDDs indirectly by inhalation of room air contaminated from cigarette smoking of their parents. In addition, older children and teenagers, may be directly exposed if they become smokers themselves. Malisch (1994) reported that some colored candle wax produced with certain dye pigments contained CDDs/CDFs. By burning these candles, CDDs could be released into room air and be an additional source of inhalation exposure for children.

Children may also be exposed to CDDs by dermal contact with some new, unwashed clothing, particularly those manufactured in some developing countries or from fabric shipped from developing countries where pentachlorophenol (PCP) is used for preserving cotton fabrics during sea transport (Horstmann and McLachlan 1994). Exposures can be reduced by washing new clothes prior to wearing.

Children could potentially be exposed to CDDs at home from a variety of incineration sources. For example, if their parents routinely burn domestic garbage containing scrap wood treated with PCP (Chiu et al. 1983) or untreated wood (Clement et al. 1985), old pesticide containers that may have contained 2,4,5 T or 2,4-D or Silvex (Arthur and Frea 1989), or polyvinylchloride (PVC) pipes or other plastics items (Lustenhouwer et al. 1980), or extensively use a wood stove (Clement et al. 1985), children may be exposed to higher levels of CDDs in outdoor and/or indoor air. Time spent in a garage where cars or trucks are being repaired and the engines are running, exposes children and teenagers to exhaust products and engine soot that may also contain CDDs (Bingham et al. 1989; Cirnies-Ross et al. 1996).

Although there are many studies on the effects of CDDs on adults that receive occupational exposures (Fingerhut et al. 1989; Hesso et al. 1992; Patterson et al. 1989a; Schecter et al. 1985a, 1994b; Tepper et al. 1997), no information was located on the potential for workers in the United States to bring CDDs home on their clothing or shoes, thus contaminating other family members, including children. It is conceivable, however, that because CDDs are present in a variety of diverse occupational settings (see Section 5.5.2 Occupational Exposures), that poor occupational hygiene could result in CDDs being brought home and contaminating domestic dwellings.

Children in populations with potentially high exposure living in the vicinity of former or current production sites where CDDs are released as by-products, (e.g., incinerators, other waste disposal facilities, and

hazardous waste sites) may be exposed to CDDs by several pathways (see Section 5.7). Children may be exposed to CDDs in CDD-contaminated soils. Dermal absorption from contaminated soil, however, is likely to be inefficient (Poiger and Schlatter 1980; Shu et al. 1988; Weber et al. 1991c). Young children are potentially exposed to CDDs because of their tendency, through hand-to-mouth activity, to ingest soils (pica) that may be contaminated with CDDs (see Section 5.7 for further details) (Fries and Paustenbach 1990; Kimbrough et al. 1984; Paustenbach et al. 1992; Pohl et al. 1995). La Goy (1987) estimated the following average soil ingestion rates for children: age 0–1 years old, 50 mg/day (maximum 250 mg/day); 1–6 years old, 100 mg/day (maximum 500 mg/day); 6–11 years old, 50 mg/day (maximum 250 mg/day); and over 11 years old, 50 mg/day (maximum 100 mg/day). If children ingest between 50 and 100 mg of soil per day (LaGoy 1987) and the soil they ingest contains 1 pg/g (1 ppt) of CDDs, a child may be exposed to 0.05-0.1 pg of CDDs per day by this pathway alone (see Section 5.7).

Children in high risk populations include children of recreational or subsistence fishers, children of subsistence hunters particularly those that consume tissues of marine mammals, and children of subsistence farmers that consume meat, milk and/or dairy products from their own farm raised animals (see Section 5.7 for further details). For example, Native American and other subsistence fishing communities may be at greater health risks from CDDs in fish and children in these population often consume larger amounts of fish than adult members of the general population (CRITFC 1994; Mott 1995). Children of recreational and subsistence fishers who routinely consume locally caught fish from CDD-contaminated waterbodies can be exposed to higher CDD concentrations than children who consume similar or larger amounts of commercially marketed fish from a variety of sources (Ebert et al. 1996; EPA 1995c; Mott 1995). The exposure to CDDs will also be highest among children who regularly eat fish as compared to those who only occasionally or never eat fish. Several recent studies have documented the higher fish consumption rates among subsistence fishers some of which are Native American populations (CRITFC 1994; Nobmann et al. 1992; Wolfe and Walker 1987). A study of fish consumption patterns among the Umatilla, Nez Perce, Yakama, and Warm Springs tribes of the Columbia River Basin in Washington and Oregon (CRITFC 1994) found that the consumption rate for these Native American children (5 years and younger) from these four tribes was 19.6 g/day (a consumption rate over 3 times higher than that for adults in the general population (6.5 g/day).

This increased exposure has been demonstrated by serum CDD levels, which are found to be several times higher in people who regularly eat fish as compared to those who occasionally or never eat fish (Anderson et al. 1998; Svensson et al. 1991) (see Sections 5.5 and 5.9). In addition, this same situation also applied

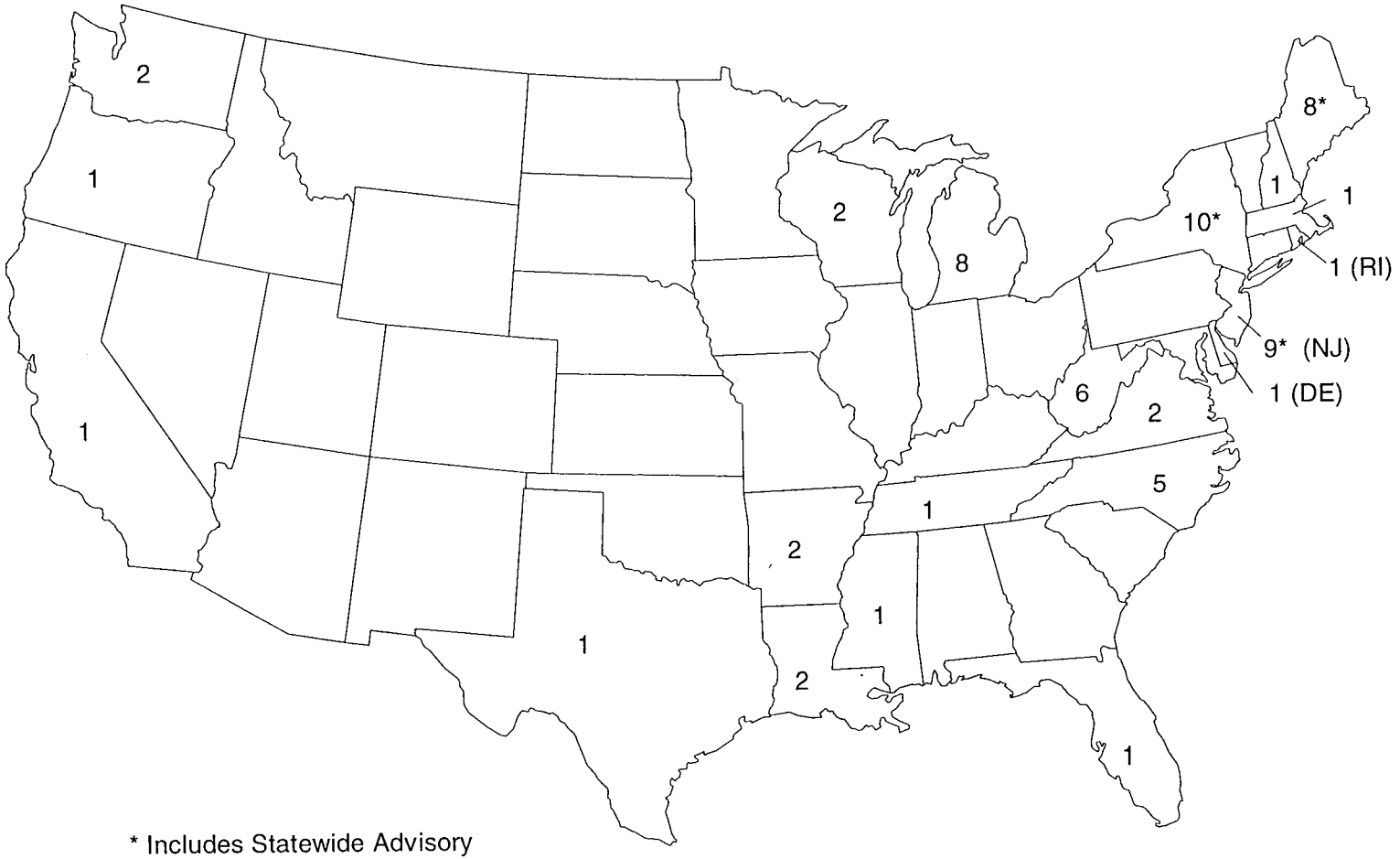
for consumption of wildlife, specifically marine mammals (Ayotte et al. 1997; Dewailly et al. 1992). Similar dietary situations exist for children of subsistence hunters that tend to consume tissues of marine mammals and children of subsistence farmers that consume beef, milk and other dairy products from their own farm raised animals. In the case of subsistence fishers, subsistence hunters, and subsistence farmers, all three populations share one problem, that the source of their fish, meat, and/or milk and other dairy products, is typically restricted to a localized area, and if these food sources are contaminated with CDDs, adults and children in these populations will be exposed to higher levels of CDDs than members of the general population (see Section 5.7 for additional details on these populations at risk).

In order to reduce exposure from consumption of CDD-contaminated fish and wildlife, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish, shellfish, and wildlife species from certain waterbodies where CDD concentrations in tissues of these species exceed the human health level of concern (EPA 1995c) (see Section 5.7 for additional information). Recreational and subsistence fishers typically consume larger quantities of fish and shellfish than the general population and frequently fish the same waterbodies routinely. Because of this, children living in these populations are at greater risk of exposure to CDDs and other chemical contaminants if the waters they fish are contaminated. Currently, 66 advisories have been issued by 21 states restricting the consumption of CDD-contaminated fish and shellfish (EPA 1998b) and one state Arkansas also has issued a consumption advisory for wood ducks, a species of migratory waterfowl. Three states (New Jersey, New York and Maine) also have statewide advisories for CDDs in their marine waters (EPA 1998a). The number of waterbodies under advisory for CDD in each state is shown in Figure 5-8.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to CDDs (Section 5.5), there are several groups within the general population with potentially high exposures (higher-than-background-normal levels) to CDDs. Historically, populations that have been exposed to higher-than-normal background levels of CDDs in the air, water, soil, and/or food have included those who were exposed to 2,3,7,8-TCDD as a result of industrial accidents (e.g., Nitro, West Virginia; and Seveso, Italy) and those exposed through environmental contamination (e.g., Times Beach, MO; Binghamton, NY; Love Canal, NY; Newark, NJ; and Vietnam) (Kahn et al. 1988; Schecter 1985; Schecter and Tiernan 1985; Schecter et al. 1987a, 1989a; Umbriet et al. 1986a, 1986b; Zook and Rappe 1994).

Figure 5-8. National Listing of Fish and Wildlife Consumption Advisories for Dioxins



* Includes Statewide Advisory

Source: EPA 1998b

Currently, individuals living in proximity to sites where CDDs are produced as chemical by-products or sites where CDD-contaminated chemicals are disposed, individuals living near municipal and industrial incinerators, and individuals living near one of the 110 NPL hazardous waste sites where CDDs have been detected in some environmental media (HazDat 1998) are at risk of receiving potentially higher-than-normal background levels of exposure. Other populations at risk of exposure primarily through dietary habits, include recreational and subsistence fishers who typically consume larger amounts of locally caught fish and shellfish than the general population, subsistence hunters, particularly those in the high latitudes, who typically consume large amounts of locally caught game including marine mammals; and subsistence farmers and their families living in areas contaminated with CDDs who exclusively consume their own farm-raised beef and dairy products.

Individuals exposed through industrial accidents or environmental contamination. Very extensive residential contamination by 2,3,7,8-TCDD occurred in Seveso, Italy, when a 2,4,5-TCP reactor exploded in 1976 (Mocarelli et al. 1991). The contaminated area was divided into three zones based on the concentration of 2,3,7,8-TCDD in the soil. Families in zone A, the most heavily contaminated area based on soil 2,3,7,8-TCDD levels, were evacuated within 20 days of the explosion and measures were taken to minimize exposure of residents in nearby zones. A recent analysis of 19 blood samples from residents of zone A, which were collected and stored shortly after the accident, showed serum lipid levels of 2,3,7,8-TCDD that ranged from 828 to 56,000 ppt. These serum lipid levels are among the highest ever reported for humans (Mocarelli et al. 1991).

In a study conducted in Missouri, 2,3,7,8-TCDD was measured in the adipose tissue of 39 volunteers with a history of residential, recreational, or occupational exposure (14 years post-exposure) and in 57 persons in a control group (Patterson et al. 1986a). Based on questionnaire responses, the eligible exposed group for this study consisted of people who were exposed either to areas with 2,3,7,8-TCDD concentrations in soil between 20 and 100 ppb for 2 or more years or to 2,3,7,8-TCDD concentrations >100 ppb for at least 6 months. Persons who met these criteria were classified as having one of three types of exposure: residential (either living in close proximity to areas with 2,3,7,8-TCDD-contaminated soil or having evidence of contamination inside the home), recreational (riding or caring for horses in 2,3,7,8-TCDD-contaminated stable arenas at least one time per week), or occupational (working either in a hexachlorophene production facility or at truck terminals where the grounds had been sprayed with 2,3,7,8-TCDD-contaminated waste oil). All study participants had detectable levels of 2,3,7,8-TCDD in their adipose tissue, but the group with known previous exposures had significantly higher levels than

controls. Nineteen (49%) of the 39 exposed persons had levels higher than the highest 2,3,7,8-TCDD concentration (20.2 ppt) detected in the 57 controls. Six (15%) of the 39 exposed persons had 2,3,7,8-TCDD concentrations >100 ppt. Five of the 6 values >100 ppt were from persons exposed to 2,3,7,8-TCDD during the production of hexachlorophene. The other high value (577 ppt) was found in a man exposed to 2,3,7,8-TCDD while horseback riding in a contaminated arena. 2,3,7,8-TCDD concentrations measured in the occupational group (average 136.2 ppt; range 3.5–750 ppt) were, in general, higher than those in the residential group (average 21.1 ppt; range 2.8–59.1 ppt), the recreational group (average 90.8 ppt; range 5.0–577 ppt), and the control group (average 7.4 ppt; range 1.4–20.2 ppt) (Patterson et al. 1986a).

2,3,7,8-TCDD has been detected at concentrations ranging from 20 to 173 ppt in adipose tissue from 3 Vietnam veterans reported to have been heavily exposed to Agent Orange (Gross et al. 1984). Except for these few men, however, 2,3,7,8-TCDD concentrations in American Vietnam and non-Vietnam veterans were nearly identical with mean serum levels of approximately 4 ppt (CDC 1988). Concentrations of 2,3,7,8-TCDD in the controls (those who never served in Vietnam) ranged from not detected (4 ppt) to 20 ppt. The veterans had served in Vietnam in 1967 and 1968 in areas where Agent Orange had been heavily used (CDC 1988). In another study, 2,3,7,8-TCDD was detected in adipose tissue of 14 Vietnam veterans and 3 control patients at levels ranging from not detected (2–13 ppt) to 15 ppt. No significant differences in the tissue levels of Vietnam veterans and the controls were found in this study (Weerasinghe et al. 1986). Air Force personnel associated with Operation Ranch Hand (spraying of Agent Orange) in Vietnam from 1962 to 1971 had serum CDD levels up to 10 ppt (521 persons). A correlation was found between CDD concentrations and increased body fat (USAF 1991). The median half-life of 2,3,7,8-TCDD in 36 veterans was estimated to be 7.1 years (Pirke et al. 1989). In 1987, many of the exposed Air Force personnel had serum CDD concentrations >50 ppt and several had concentrations exceeding 300 ppt (CDC 1987). Wolfe et al. (1994) reported a half-life value of 11.3 years for Air Force personnel involved in Operation Ranch Hand. Using individuals from two rice oil poisoning episodes (Yusho [Japan] and Yu-Cheng [Taiwan]), Ryan et al. (1993a) have shown that the elimination of related CDFs is not constant, but variable, with faster clearance at higher doses followed by a slowing down in the rate of loss as body burden decreases. By analogy, the same may be true for CDDs. It is also likely that individual congeners or those with the same degree of chlorination are excreted from the body at rates that differ from those estimated for 2,3,7,8-TCDD. Because the rate of clearance is not constant, uncertainty in determining the half-life measurement may result, especially for estimates of the changing body burden of total CDDs measured as TEQs.

Individuals living in proximity to production or disposal sites. Individuals living in the vicinity of former or current production sites where CDDs are released as by-products, (such as incinerators, coal-fired electric generating facilities, other waste disposal facilities, and hazardous waste sites) may be exposed to CDDs from several exposure pathways. CDDs have been detected in soil at 94 of the 126 sites where they have been detected in some environmental media (HazDat 1998).

Children and adults may receive higher CDD exposures from dermal contact if they play or work with CDD-contaminated soils. Several studies have examined the bioavailability of 2,3,4,7-TCDD for uptake by dermal exposure. In a study using *in vitro* human skin tissue, 2,3,7,8-TCDD did not readily penetrate into the human skin and the vehicle of exposure played an important role in the dermal penetration (Weber et al. 1991c). These authors reported that when the exposure vehicle was acetone, the maximum 2,3,7,8-TCDD penetration into the *in vitro* human stratum corneum (30–45% of the dose) was reached within 100 minutes, with a tendency to decrease after 1,000 minutes. Using mineral oil as the exposure vehicle, absorption of 2,3,7,8-TCDD leveled off at 10% of the dose, and it took more than 300 minutes to reach the maximum. The data suggest that the rates of absorption of 2,3,7,8-TCDD into *in vitro* human skin are moderate (worst-case scenario) to low when the 2,3,7,8-TCDD is applied in acetone; when applied in mineral oil, the adsorption rate was further reduced. Shu et al. (1988) reported that in rats, dermal absorption of 2,3,7,8-TCDD in a soil vehicle was only 1% of the administered dose. Similarly, Poiger and Schlatter (1980) reported that in rats, dermal absorption of 2,3,7,8-TCDD was almost eliminated when soil or activated carbon was used as vehicles. These data support the original Kimbrough et al. (1984) risk assessment of a contaminated site in which the authors estimated that the additional lifetime uptake of TCDD from soil above background uptake will consist of 95% from soil ingestion, 3% from dermal exposure to soil (assuming 1% dermal absorption), and 2% from inhalation of soil particles.

Children and adults also may receive potentially higher oral exposures from ingestion of CDD-contaminated soils from their unwashed hands while playing or working in CDD-contaminated areas (Fries and Paustenbach 1990; Kimbrough et al. 1984; Paustenbach et al. 1992; Pohl et al. 1995). Bioavailability is an integral factor in the estimation of the internal dose (or dose at the target tissue) of the chemical. Like dermal absorption, gastrointestinal absorption of 2,3,7,8-TCDD and related compounds is variable, incomplete, and congener- and vehicle-specific (see Section 2.3.1). More lipid soluble congeners, such as 2,3,7,8-TCDF, are almost completely absorbed, while the extremely insoluble OCDD is poorly absorbed. However, laboratory data suggest that there are no major interspecific differences in the gastrointestinal absorption of CDDs and CDFs. Results from animal studies indicate that bioavailability of 2,3,7,8-TCDD

from soil varies between sites because CDDs bind tightly to soil, and increasingly so with the passage of time and clay content of the soil (Gough 1991; Umbreit et al. 1986a;1986b). Therefore, 2,3,7,8-TCDD soil concentrations alone may not be indicative of the potential for human health hazard from contaminated soils, and site-specific evaluation may be essential. In their risk assessments, Kimbrough et al. (1984) assumed 30% bioavailability from ingestion of soil, but they point out that animal studies with contaminated Missouri soil indicated absorption as high as 30 to 50% (McConnell et al. 1984). Pohl et al. (1995) assumed 40% bioavailability of 2,3,7,8-TCDD from soil. In contrast, Paustenbach et al. (1986) assumed only 10–30% bioavailability. However, unless toxicokinetic studies that use soil samples from the specific site are available, it is difficult to speculate on how much 2,3,7,8-TCDD as well as other CDDs will be bioavailable. ATSDR's policy on CDDs contaminated soils is in Appendix B of this profile.

Individuals may also receive higher doses from routine consumption of CDD-contaminated fish from local waters receiving runoff or leachates from the waste site (Paustenbach et al. 1992). CDDs have been detected in fish collected at 12 of the 126 NPL sites where they have been detected in some environmental media (HazDat 1998).

Lastly, individuals living near incinerator or hazardous waste sites may inhale vapors or particulates contaminated with CDDs from ambient outdoor air. This, however, would be a relatively minor exposure pathway as only about 50% of all particles are of inhalable size (<10μm) (Fries and Paustenbach 1990; Paustenbach et al. 1992). These authors concluded that since uptake of 2,3,7,8-TCDD from foods will be approximately 500–1,000-fold greater than that due to inhalation, that inhalation exposure was a relatively insignificant exposure pathway even for individuals living in proximity to an incinerator.

Recreational and subsistence fishers. In general, concentrations of CDDs in sport fish and shellfish from CDD-contaminated waters can be at least an order of magnitude higher than in commercial fish and shellfish purchased in a supermarket (see Section 5.4.4). Since CDDs have been found in fish from contaminated lakes and streams (Crunkilton et al. 1987; De Vault et al. 1989; EPA 1987n, 1992; Kuehl et al. 1989, 1994; Niimi and Oliver 1989a, 1989b; Reed et al. 1990) and fish and shellfish from estuarine waters (Bopp et al. 1991; Brown et al. 1994; Cai et al. 1994; Hauge et al. 1994; Rappe et al. 1991), populations that consume large quantities of fish or shellfish from these contaminated waters are also likely to have higher exposures to CDDs, although the method of preparation (edible fillets versus skin-on fillets or whole fish) and cooked versus raw consumption may substantially reduce the amount of CDDs ingested (Paustenbach et al. 1992; Schecter et al. 1996c).

Recreational (sport) and subsistence fishers (including some native American peoples) who consume locally caught fish from CDD-contaminated waterbodies can be exposed to higher CDD concentrations than individuals who consume similar or larger amounts of commercially marketed fish from a variety of sources (Ebert et al. 1996; EPA 1995c). The exposure to CDDs will also be highest among people who regularly eat large amounts of fish as compared to those who only occasionally or never eat fish. This increased exposure has been demonstrated by serum CDD levels to be several times higher in people who regularly eat fish as compared to those who occasionally or never eat fish (Anderson et al. 1998; Svensson et al. 1991).

Several studies suggests there is a correlation between consumption of CDD-contaminated fish and/or marine mammal tissues and elevated levels of CDDs in blood (Anderson 1998; Ayotte et al. 1998; Svensson et al. 1991). Svensson et al. (1991) reported elevated blood levels of CDDs in Swedish fish consumers living near the Baltic Sea. Three distinct groups of consumers were studied: individuals who did not consume any fish, moderate fish consumers (consumption rate of 220–500 g of fish/week [31–71 g/day]), and high fish consumers (consumption rate of 700–1,750 g of fish/week [100–250 g/day]). The highest fish consuming group was composed of fishermen or workers in the fishing industry who consumed primarily salmon (30–90 pg TEQ/g) and herring (8–18 pg TEQ/g) from the Baltic Sea. The TEQ blood level was found to average 63.5 pg TEQ/g lipid for the high consumption group, 25.8 pg TEQ/g lipid for the moderate consumption group, and 17.5 pg TEQ/g lipid for the nonfish-eating group. With respect to 2,3,7,8-TCDD blood levels, the mean blood level detected was 1.8 pg/g (lipid basis) for individuals that consumed no fish, 2.5 pg/g for the moderate consumers, and 8.0 pg/g for the high consumer group. It should be noted that even in those individuals who consumed no fish, detectable levels of CDDs were present in their blood. This indicates that other food sources (e.g., meat, milk, and other dairy products) are likely to be important contributors to the total body burden of CDDs (Rappe 1992).

Recently, Anderson et al. (1998) completed a preliminary study of the levels of 8 CDDs, 10 CDFs, 36 PCBs, and 11other persistent organochlorine pesticides in human serum samples from Great Lakes sport fish consumers. Overall, the 31 fishers on average consumed 49 Great Lakes sport fish meals per year, for a mean of 33 years. This is in contrast to the general population in the Great Lakes basin that typically consumes 6 meals of Great Lakes sport fish per year. A summary of the distribution of CDDs is provided in Table 5-14. CDD congeners detected most often were 1,2,3,4,6,7,8-HpCDD (31 detects), OCDD (31 detects), 1,2,3,6,7,8-HxCDD (30 detects), 2,3,7,8-TCDD (25 detects) and 1,2,3,7,8-PeCDD (20 detects). The overall mean concentration for 2,3,7,8-TCDD was 6.6 ppt. Total CDD concentrations were highest

Table 5-14. Mean and Range (ppt) of Serum CDD (Lipid Adjusted)

Dioxin congener	All subjects (n=3)	Lake Michigan (n=9)	Lake Huron (n=11)	Lake Erie (n=11)	Comparison group[a]
2,3,7,8-TCDD[b]	6.6 (ND–17.2)	4.7 (ND–7.9)	10.5 (4.4–17.2)	4.3 (ND–9.0)	2.8 (0.3–8.9)
1,2,3,7,8-PeCDD[b]	10.4 (ND–31.5)	9.8 (ND–23.7)	16 (ND–31.5)	5.8 (ND–12.3)	6.6 (0.6–14.1)
1,2,3,4,7,8-HxCDD	8.4 (ND–22.7)	11.4 (ND–16.3)	8.4 (2.1–22.7)	6.6 (ND–16.6)	9.0 (0.9–121)
1,2,3,6,7,8-HxCDD	126 (71.9–228)	120 (71.9–190)	142 (88.7–228)	115 (85.1–150)	70.8 (24.8–160)
1,2,3,7,8,9-HxCDD	7.0 (ND–22.8)	8.7 (ND–22.8)	6.5 (ND–16.1)	5.8 (ND–13)	9.4 (0.9–25.8)
1,2,3,4,6,7,8-HpCDD[b]	134 (34.9–314)	144 (72.5–204)	163 (86.7–314)	95.9 (34.9–179)	124 (29.1–358)
1,2,3,4,6,7,9-HpCDD[c]	[c]	ND	ND	[c]	4.4 (1.0–29.1)
OCDD	777 (297–1,869)	793 (409–1,587)	919 (371–1,869)	623 (297–981)	971 (286–2,710)
Dioxin total (ppt)	1,062 (453–2,410)	1,087 (615–2,017)	1,259 (729–2,410)	844 (453–1,286)	1,198[d]
Dioxin EPA TEQs[b]	27.5 (8.2–58.7)	25.9 (13.8–38.3)	36 (18.5–58.7)	20.7 (8.2–31.0)	15.5[d]

[a] Unexposed sample residing in Jacksonville, Arkansas (n=70)
[b] Three Great Lakes subgroups are statistically different ($p<0.03$)
[c] One observation detected
[d] Range not available

CDDs = chlorinated dibenzo-*p*-dioxins; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; ND = none detected; OCDD = octachlorinated dibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ=toxicity equivalency concentration.

Source: Anderson et al. 1998

for Lake Huron fish consumers (1,259 ppt), intermediate for Lake Michigan consumers (1,087 ppt) and lowest for Lake Erie consumers (844 ppt). The comparison group serving as a control included individuals residing in Arkansas and had a total CDD serum concentration of 1,198 ppt. With respect to the TEQ values for CDDs, the pattern among Great Lakes fish consumers was similar to that for total CDD consumers with TEQs for Lake Huron fish consumers of 36 ppt, Lake Michigan consumers of 25.9 ppt, and Lake Erie consumers of 20.7 ppt. The TEQ values for the three Great Lakes sport fish consumer groups were statistically different ($p<0.03$). Although the comparison population had CDD concentrations within the range of the Lake Michigan and Lake Huron fish consumers, the TEQ value for CDDs for this population was the lowest of the four groups at 15.5 ppt. The authors concluded that Great Lakes anglers who are life-long frequent consumers of sport fish represent a subpopulation with the potential for significant exposure to CDDs as well as CDFs and PCBs. The levels of CDDs, CDFs, and PCBs found in sportfish and human tissue residues were above those in the general population.

Ayotte et al. (1998) measured concentrations of CDDs/CDFs and PCBs in plasma of adult Inuit living in Arctic Quebec, Canada. The Inuit consume large amounts of fish and marine mammal tissue. The mean concentration of 2,3,7,8-TCDD was 8.4 ppt (range 2.5 to 36.0 ppt) in the Inuit population and < 2 ppt (range <2) for the control population in Southern Quebec. The TEQ values for all CDDs/CDFs was 39.6 ppt (range 17.1 to 81.8 ppt) in the Inuit population and 14.6 ppt (range 11.5 to 18.9 ppt) for the control population. When PCBs and CDDs/CDFs are considered together, the mean TEQ values for all dioxin-like compounds was 184.2 ppt in the Inuit population (range 55.8 to 446.7 ppt) and 26.1 ppt (range 20.1 to 31.7 ppt) for the control population.

Several recent studies have documented the higher fish consumption rates among subsistence fishers some of which are Native American populations. In a study of Alaskan subsistence economies, Wolf and Walker (1987) reported daily fish consumption rates ranging from 6 to 1,536 g/day, with an average consumption rate of 304 g/day. This average consumption rate for subsistence fishers is more than 46 times higher than the mean fish consumption rate of 6.5 g/day estimated for the general population (EPA 1995c). In a study of 11 Alaskan communities, Nobmann et al. (1992) reported an average daily fish consumption rate of 109 g/day. This is more than 16.8 times higher than the mean fish consumption rate of 6.5 g/day estimated for the general population (EPA 1995c). A recent study of fish consumption patterns among the Umatilla, Nez Perce, Yakama, and Warm Springs tribes of the Columbia River Basin in Washington and Oregon (CRITFC 1994) found that adults in these 4 tribes consume an average of 58.7 g/day of fish and the 95th percentile of fishers consume 170 g/day of fish. This mean consumption rate is more than nine times

higher than the mean fish consumption rate estimated for the general population (EPA 1995c). Fitzgerald et al. (1995) conducted a study to establish patterns of fish consumption of nursing Mohawk Indians residing in the vicinity of three hazardous waste sites located near Akwesasne, NY, compared to a control population of Caucasian women in New York state. The dietary data showed that there was a significant past prevalence of local fish consumption among Mohawk mothers (23.5 meals per year) more than a year before pregnancy as compared to the controls (14.1 meals per year).

In order to reduce CDD exposure from consumption of CDD-contaminated fish and shellfish, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish and shellfish species from certain waterbodies where CDD concentrations in fish and shellfish tissues exceed the human health level of concern. This level of concern is set by individual state agencies, but many states use the FDA tolerance levels of >25 ppt, but <50 ppt to advise consumers to restrict consumption and levels >50 ppt to issue advisories recommending no consumption of contaminated fish and shellfish (see Table 7-1). These values are used despite the fact that they were designed to protect consumers from the health risks associated with consumption of fish and shellfish that are shipped in interstate commerce and are purchased in commercial markets. In 1995, the EPA Office of Water issued guidance to states on sampling and analysis procedures to use in assessing the health risks from locally caught fish and shellfish. The risk assessment method proposed by EPA was specifically designed to assist states in developing fish consumption advisories for recreational and subsistence fishers (EPA 1995c). These two groups within the general population consume larger quantities of fish and shellfish than the general population and frequently fish the same waterbodies routinely. Because of this, these populations are at greater risk of exposure to CDDs and other chemical contaminants if the waters they fish are contaminated. The EPA advises states to use a screening value of $7x10^{-7}$ ppm (0.7 ppt) of total TEQ value (wet weight) in fillets for the general population as a criteria to evaluate their fishable waterbodies (EPA 1995c). Currently, 66 advisories have been issued by 21 states restricting the consumption of CDD-contaminated fish and shellfish (EPA 1998b). Three states (New Jersey, New York, and Maine) also have statewide fish advisories in effect for their marine coastal waters. In addition, the State of Arkansas also has issued a wildlife advisory for wood ducks, a species of waterfowl in Bayou Meto, a site contaminated by a point source discharge (White and Hoffman 1995). The number of waterbodies under advisory for CDD in each state is shown in Figure 5-8.

Subsistence hunters. Native American populations such as the Inuit of Alaska and other subsistence hunters (particularly those living in high latitude areas of the United States) may have higher exposure to

CDDs in marine mammals, but not terrestrial mammals (i.e., caribou). CDDs have been detected in seal and polar bear fat and liver tissues (Norstrom et al. 1990). Recently, Ayotte et al. (1997) reported that in 20 pooled samples of Inuit blood, the TEQ concentration supplied by CDDs/CDFs (combined) was 39.6 ppt as compared to 14.6 ppt in 3 pooled samples of blood from individuals in the general population in Southern Quebec. The mean 2,3,7,8-TCDD concentrations were 8.4 ppt for Inuit and <2 ppt for members of the general population. When planar PCBs, mono- and di- ortho PCBs were added, the mean TEQs were 184.2 ppt and 26.1 ppt, respectively, for Inuit and members of the general population in Southern Quebec. In a related study, Dewailly et al. (1992) found that breast milk of these Inuit was more contaminated by CDDs, CDFs, and PCBs than milk of women in Southern Quebec. For CDDs and CDFs, differences were less impressive than for PCBs. However, mean OCDD concentrations were 292 ppt versus 132 ppt and 2,3,7,8-TCDD concentrations were 6.2 ppt versus 2.3 ppt for Inuit women and women in Southern Quebec, respectively. Concentrations of OCDD and 2,3,7,8-TCDD were 2 to 3 times greater among the native Inuit population that consumed large amounts of fish and marine mammal tissue. No data were located specifically for CDD concentrations in the adipose tissue, blood, or breast milk of native American populations in the United States. However, by analogy to CDDs in Canadian Inuit populations, it is anticipated that CDD concentrations in these tissues are likely to be higher among individuals who routinely consume large quantities of wild game species, especially marine mammal than among members of the general population.

In a study of subsistence economies in the State of Alaska, Wolfe and Walker (1987) reported that total annual per capita consumption of wild game species (including land mammals, marine mammals, and fish) ranged from 10 to 1,498 pounds (median harvest of 252 pounds) as compared to 222 pounds of meat, fish, and poultry consumed each year by individuals in the western United States. In the 1980s, the 98 Alaskan subsistence communities surveyed harvested wild game at levels from one-half to 4 times the U.S mean. The average daily per capita consumption was 0.67 pounds for fish and 0.23 pounds for land mammals based on all 98 communities, and 0.2 pounds for marine mammals based on the 41 coastal communities surveyed. Land mammals consumed in these communities included moose, caribou, deer, black bear, snowshoe and tundra hare, beaver, and porcupine; while marine mammals included seal, walrus and whales. Subsistence hunters and their families are a population at potentially higher risk of CDD exposure when the wild game species particularly marine mammals they consume are contaminated with CDDs. It should be noted that concentrations of CDDs/CDFs were recently determined in caribou tissue samples from 7 herds across the Canadian Arctic (Hebert et al. 1996). In contrast to levels of 2,3,7,8-TCDD found in marine mammals which ranged from 2 to 37 ng/kg (ppt wet weight) (Norstrom et al. 1990),

concentrations of 2,3,7,8-TCDD in caribou were extremely low, sub ng/kg (lipid basis). 2,3,7,8-TCDD was detected in adipose tissue samples of two herds in the eastern Canadian Arctic at levels of 0.73 and 0.14 ng/kg, but was not detected in tissue samples from other herds at detections limits as low as 0.03 ng/kg (lipid basis). CDFs were detected at sub-ng/kg levels in all cases. TEQs were dominated by non-ortho substituted PCBs in all cases, and ranged from 0.33 ng/kg to 3.3 ng/kg in adipose tissue. The authors concluded that caribou tissues are therefore less contaminated than tissues from marine mammals.

Subsistence farmers that consume their own farm-reared meat and dairy products.

Subsistence farmers and their families living on farms where CDD concentrations may be high who exclusively eat meat and dairy products produced on their own farms may be exposed to higher levels of CDD in these foods than the general population. Grazing cattle in farming areas downwind of municipal or industrial incinerators where CDDs may be deposited as particulates on soil or forage crops or grazing cattle in areas with CDD-contaminated soil or soil amended with municipal sewage sludges or paper mill sludges contaminated with CDDs may result in higher CDD tissue residues in the animals (EPA 1991b; Fries and Paustenbach 1990). In an evaluation of potential transmission of 2,3,7,8-TCDD from incinerator emissions to humans via foods, Fries and Paustenbach (1990) determined that the amount of 2,3,7,8-TCDD accumulated in soil from airborne emissions was less important that the amount deposited in forage. These authors further concluded that the airborne emissions of CDDs/CDFs from modern waste incinerators that have appropriate air pollution devices should not pose a significant health hazard regardless of the incinerator location. The authors, however, acknowledged that it would be desirable to measure 2,3,7,8-TCDD in soil and crops around existing facilities to better evaluate their assessment results, although they felt it was likely that concentrations would be too low to reliably quantify. More recently, Fürst et al. (1993) reported that soil levels up to 30 pg TEQ/g dry matter did not result in elevated CDD concentrations in cow's milk. However, these authors did show increasing concentrations of CDDs in grass resulted in slightly higher CDD concentrations in cow's milk. These authors, like Fries and Paustenbach (1990), believe that the pathway of air to grass to cow is more important than the pathway of soil to grass to cow.

In a European survey of cow's milk samples collected on dairy farms, elevated CDD/CDF milk concentrations were used to pinpoint the existence of certain "hotspots" of CDD contamination. These "hotspots" were generally found near CDD/CDF emitting sources, such as cable waste incinerators or metal refining industries (Beck et al. 1990; Liem et al. 1991; Rappe et al. 1987). Riss et al. (1990) analyzed blood from one farmer in a CDD/CDF-contaminated location in proximity to a metal reclamation

plant who consumed milk produced from his own farm, and found 2,3,7,8-TCDD blood levels (55 pg/g on a lipid basis) above expected background levels.

Exposure to 2,3,7,8-TCDD from land application of municipal sewage sludge or paper mill sludge also can occur through the dietary pathway if people consume food grown or animals grazed on sludge-amended lands (EPA 1991b). Wild et al. (1993), using a human exposure assessment model, predicted that if all the produce consumed by a human is derived from agricultural land to which sewage sludge is applied at a rate of 10 tons/hectare and 0.5 ng/kg dry weight concentration, this would increase exposure to 2,3,7,8-TCDD by 0.0332 ng/day or 39% over background conditions. This scenario assumes that the poultry, eggs, and fish CDD concentrations are unaffected by the sludge application. Most recently, McLachlan et al. (1994) reported that the prolonged use of sewage sludge as a soil amendment on English farms under some conditions can lead to an increase in the concentrations of CDDs/CDFs in both the soil and in cow's milk. Subsistence farmers and their families are a population at potentially higher risk of CDD exposure because meat and dairy products are substantial sources of CDDs in the U.S. diet (Schecter et al. 1994e, 1996a).

5.8 ADEQUACY OF THE DATABASE

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

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

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of 2,3,7,8-TCDD are sufficiently characterized to predict the environmental fate of 2,3,7,8-TCDD (IARC 1977; Sax and Lewis 1987; Schroy et al. 1985; Shiu et al. 1988). Of all the CDDs, 2,3,7,8-TCDD has been the compound most studied. Not all isomers within each homologous class have been equally well studied for many of the physical and chemical properties. Information on physical and chemical properties of certain congeners (particularly 1,2,3,7,8,-PeCDD and 1,2,3,6,7,8-HxCDDs) would be helpful in better understanding the different fate and transport pathways of the homologous groups.

Production, Import/Export, Use, Release, and Disposal. CDDs are not manufactured commercially in the United States except on a laboratory scale for use in chemical and toxicological research (Cambridge Isotope Laboratories 1995). They are produced as undesired by-products during the manufacture of chlorophenols (e.g., PCP and 2,4,5-trichlorophenol) and during combustion processes (IARC 1977; NTP 1989; Podoll et al. 1986). CDDs are ubiquitous in the environment and have been found at low levels (ppt or lower) in air, water, soil, sediment, and foods. Current disposal methods are efficient and are subject to EPA and state regulations.

According to the Emergency Planning and Community Right-To-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1994, became available in May of 1996. This database will be updated yearly and should provide a list of industrial production facilities and emissions. However, there are no TRI data for CDDs since CDD releases are not required to be reported (EPA 1995g).

Environmental Fate. CDDs are subject to atmospheric transport and both wet and dry deposition (Kieatiwong et al. 1990). They are partitioned to air, water, sediment, and soil, and they accumulate in both aquatic and terrestrial biota. CDDs can volatilize to the atmosphere from water and soil surfaces. They adsorb strongly to soils and are not likely to leach into groundwater (Eduljee 1987b). In the aquatic environment, CDDs partition to sediment or suspended particulates. TCDD, HpCDD, and OCDD are subject to photolysis in air, water, and soil (Plimmer et al. 1973). 2,3,7,8-TCDD is biodegraded very slowly in soil and thus is likely to persist in the soil. A better understanding of environmental behavior of CDDs is needed with respect to the importance of vapor-phase versus particulate transport, the

environmental behavior of different congeners, and the significance of processes that reintroduce CDDs into the atmosphere after deposition. Information regarding the degradation of other congeners, specifically OCDD, and their degradation products in water, sediment, and soil would be useful in evaluating the various pathways of human exposure.

Bioavailability from Environmental Media. Toxicokinetic data in humans regarding adsorption of CDDs following oral and dermal exposure are very limited (Poiger and Schlatter 1986). CDDs can be absorbed following oral exposure in both humans and animals (Birnbaum and Couture 1988; Fries and Marrow 1975; Koshakji et al. 1984; Norback et al. 1975; Olson et al. 1980b; Piper et al. 1973; Poiger and Schlatter 1980). The more highly chlorinated CDD congeners are absorbed to a lesser extent than 2,3,7,8-TCDD (Koshakji et al. 1984). Also, limited information is available on the bioavailability from fly ash (Van den Berg et al. 1983, 1985). 2,3,7,8-TCDD can be adsorbed following dermal contact (Banks and Birnbaum 1991; Poiger and Schlatter 1980; Shu et al. 1988); however, dermal absorption of 2,3,7,8-TCDD from soil is very low (Shu et al. 1988). More information is needed regarding oral and dermal exposure to determine the bioavailability of CDDs from food, water, and soil. Additional information is needed to examine the discrepancy noted in the mass balance from CDDs ingested from foods and eliminated in feces. For inhalation exposure, information on the bioavailability from fly ash and sediments would be useful. Information is also needed on the selective uptake of the 2,3,7,8-substituted CDD congeners.

Food Chain Bioaccumulation. CDDs are bioconcentrated in aquatic organisms, plants, and terrestrial animals. Shellfish (including crustaceans and bivalve mollusks) appear to accumulate CDDs nonselectively to relatively high concentrations in their tissues (Bopp et al. 1991; Brown et al. 1994; Cai et al. 1994; Conacher et al. 1993; Hauge et al. 1994; Rappe et al. 1991). In contrast, finfish appear to selectively accumulate primarily 2,3,7,8-TCDD and other 2,3,7,8-substituted isomers in their tissues (Rappe et al. 1991). Information from a larger number of species on the retention of 2,3,7,8-substituted CDD congeners and general information on retention and distribution of other CDDs would be useful in better understanding both aquatic and terrestrial food chains.

Exposure Levels in Environmental Media. CDDs have been detected in air, water, soil, sediment, plant material, and foods. Environmental monitoring studies show that the higher chlorinated CDDs are usually the ones most commonly found in environmental samples (Christmann et al. 1989b; Clement et al. 1985, 1989; Pereira et al. 1985; Reed et al. 1990; Tashiro et al. 1989a; Tiernan et al. 1989b). Current

monitoring studies are needed to determine CDD levels in media surrounding hazardous waste sites. Using a model, the total average daily intake of 2,3,7,8-TCDD (by air, water, and food) for the general population was estimated to be 0.05 ng/day (range 0.008–0.3 ng/day) (Travis and Hattemer-Frey 1987). Schecter et al. (1994d, 1994e, 1996a) and Schecter and Li (1997) have provided current information on CDD exposures from food. Food consumption accounts for over 90% of background human exposure to 2,3,7,8-TCDD and other CDDs/CDFs in the general U.S. population (Hattemer-Frey and Travis 1989; Schaum et al. 1994). The average daily intake by nursing infants in the United States has been estimated to be 83 pg TEQs/kg (Schecter and Gasiewicz 1987a, 1987b).

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

Exposure Levels in Humans. CDDs/CDFs have been found in blood (Fingerhut et al. 1989; Needham et al. 1991; Päpke et al. 1989b, 1992, 1993), adipose tissue (Orban et al. 1994; Patterson et al. 1986a; Ryan et al. 1986; Schecter et al. 1986b; Stanley 1986; Stanley et al. 1986), and breast milk of both the general population and workers exposed through industrial accidents or environmental contamination (Fürst et al. 1992; Pluim et al. 1993a; Ryan et al. 1993b; Schecter and Gasiewicz 1987b; Schecter and Tiernan 1985a; Schecter et al. 1986a, 1986b; 1989e). Levels of 2,3,7,8-TCDD as well as other CDDs are generally higher in occupationally exposed individuals or those individuals exposed through industrial accidents or environmental contamination (Kahn et al. 1988; Schecter et al. 1986b; Schecter and Tiernan 1985; Schecter et al. 1987a; Umbriet et al. 1986a, 1986b). CDDs have also been detected in breast milk and blood of Canadian populations of native Inuit that consume large amounts of fish and marine mammals (Ayotte et al. 1997; Dewailly et al. 1992). Additional biological monitoring data are needed, however, for those U.S. populations surrounding hazardous waste sites or municipal, medical, or industrial incinerators, for urban versus rural exposures, and for other potentially exposed populations including subsistence fishers and hunters (Liem et al. 1991; Startin et al. 1989; Wuthe et al. 1993). Information on tissue levels in the general population worldwide are for the most part lacking (Schecter et al. 1991a). As they are identified, exposed populations should be evaluated to characterize exposure levels and health effects. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children in the general population are exposed to CDDs primarily through dietary exposures *in utero* via placental blood and in newborn infants via breast-feeding. Despite the fact that studies on the concentrations of CDDs in human breast milk have been conducted in various other countries, there is a need to determine the levels of CDDs in human milk in the United States. Additional exposure studies also are needed to determine whether dietary modifications in mothers can reduce total CDD exposures in newborns and whether dietary modifications of the infant can also reduce lifetime exposure. For children in populations with potentially high exposure to CDDs, the primary exposure pathway is through their diet; however, additional exposure to CDDs via consumption of contaminated groundwater, contaminated soil, and dermal exposure to contaminated soil may increase their exposure levels. Studies of workers in various industrial settings that are exposed to CDDs (i.e., elevated CDD levels in adipose or blood serum) should be conducted to determine whether CDDs are routinely brought home by these workers on their clothing and shoes to assess in order to determine whether this is an important exposure route for children.

Schecter and Li (1997) have calculated weight-adjusted intakes of CDDs derived from consumption of four types of fast foods for 6-year-old children. Additional information on dietary intake of CDDs from other types of foods should be conducted for various age groups of children to help identify the magnitude and sources of dietary exposure during childhood. Studies to verify these calculations would be helpful in assessing health risks to children.

The primary childhood specific means to decrease exposure to CDDs involves placing the infant on a cow's milk or soy-based baby formula and on maintenance of children on a long-term diet that is lower in animal fats (meat, dairy products, and fish) and higher in grains, fruits, and vegetables. It should be noted however, that because of the relatively short period of intake and the accepted benefits of breast-feeding that maintenance of children on long-term diet low in animal fat would likely be more beneficial in decreasing total lifetime CDD body burdens than cessation of breast-feeding. Additional means of reducing CDD exposures also should be investigated.

Exposure Registries. Approximately 250 members were enrolled in the 2,3,7,8-TCDD Subregistry of the National Exposure Registry in 1991 (ATSDR 1996). These individuals were chosen because they participated in one or more of the Missouri Dioxin Health Studies and were reportedly exposed to CDDs at one of the four Times Beach, MO area CDD sites. Data collected for each member of the Dioxin Subregistry include demographic information, smoking and occupational histories, and self-reported

responses to 25 general health status questions. The data files for the Subregistry are established at the time baseline data are collected. A follow-up survey is conducted 1 year after baseline data collection, and surveys are, in most cases, conducted at 2-year intervals after that to update the files. For the Dioxin Subregistry, all interviews are conducted by means of computer-assisted telephone interviewing. Subregistry members will be questioned yearly about their health over the previous year. This activity is carried out by ATSDR. The data will become part of public-user data files maintained by ATSDR. 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 the exposure to this compound.

The Air Force maintains an exposure registry of about 1,200 personnel previously involved in the spraying of Agent Orange (USAF 1991). The Air Force Health Study (AFHS) is an epidemiologic investigation of the association between occupational exposure to Agent Orange (and its CDD contaminants) and long-term adverse health effects experienced by Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971 and sprayed Agent Orange from fixed winged aircraft. A comparison group, which was formed from Air Force veterans, is used as the unexposed cohort. Evaluations were performed in 1982, 1985, and 1987. In the 1987 examination, 1,670 participants were involved. Health outcomes were evaluated with respect to serum CDD levels. Additional evaluations are planned for 1997 and 2002.

5.8.2 Ongoing Studies

The EPA is currently conducting a reassessment of the risk from exposure to CDDs, and other chlorinated dioxin-like compounds such as CDFs and PCBs. This reassessment involves a literature reevaluation of existing studies and new laboratory studies addressing health and ecological risks from exposure to these compounds (LaFleur et al. 1990; Rappe 1992; Schecter et al. 1994d). Currently, the EPA dioxin reassessment document is undergoing final review.

The National Institute of Environment Health Sciences and the Centers for Disease Control and Prevention are measuring levels of CDDs, CDFs, PCBs and other chemicals in blood of members of the general U.S. population as part of the NHANES program.

In addition, an international “Dioxin” research conference meets annually to discuss developments regarding these environmental contaminants. The proceedings of this international symposium on CDDs and related compounds are published annually in extended abstract form and frequently in a proceedings

issue of the journal Chemosphere and are an extensive source for papers on a wide variety of environmental and health issues related to CDDs and dioxin-like compounds.

A search of Federal Research in Progress (FEDRIP 1998) identified numerous research studies that are currently being conducted that may fill some of the data needs discussed in Section 5.7.1 (see Table 5-15).

Table 5-15. Ongoing Studies on Environmental Fate and Treatment of CDDs

Investigator	Affiliation	Title	Sponsor
Bunge AL	Colorado School of Mines Golden, CO	Dermal Adsorption from Soils—Evaluation and Prediction	National Institute of Environmental Health Sciences
Cooper K	Rutgers University New Brunswick, NJ	Effects of Polychlorinated: Dioxins, Furans, and PCBs on Aquatic Animals and Humans	U.S. Department of Agriculture
Dasinger AM	Geophex, Ltd. Raleigh, NC	Development of a Two State Bioremediation Technology for Dioxin Contaminated Soils	U.S. Air Force
Eskenazi B	University of California, Berkeley CA	Endometriosis and Dioxin Exposure in Females of Seveso	National Institute of Environmental Health Sciences
Fynes G	British Coal Corporation: Coal Research Establishment Stoke Orchard, Cheltenham, England	Emissions of Environmental Concern from Coal Utilization	European Coal and Steel Community (ECSC); British Coal Corporation; Department of Trade and Industry
Hodko D	Lynntech, Inc. College Station, TX	In Situ Degradation of Dioxins by Chemical Oxidation	U.S. Air Force
Hites RA	Indiana University, School of Public and Environmental Affairs Bloomington, IN	Toxic Organic Compounds from Energy Production	U.S. Department of Energy
Hites RA	Indiana University, School of Public and Environmental Affairs Bloomington, IN	A Global Mass Balance for Chlorinated Dioxins and Dibenzofurans	National Science Foundation
James MO	University of Florida Gainesville, FL	Bioavailability of Superfund Chemicals	National Institute of Environmental Health Sciences
Kang HK	Department of Veterans Affairs, Medical Center Washington, DC	Army Chemical Corp Vietnam Veterans Health Study	Department of Veterans Affairs,
Newsted JL	University of Massachusetts Forestry and Wildlife Management Amherst, MA	The Evaluation of Halogenated Aromatic Hydrocarbons in Fish from the Connecticut River Basin, MA	U.S. Department of Agriculture
Shaub W	Solid Waste Association of North Carolina Silver Spring, MD	Mercury and Dioxin in Waste Streams	U.S. Department of Energy
Wolff MS	Mount Sinai School of Medicine of CUNY New York, NY	Core–Exposure Assessment Providing chemical analyses for PAH and TCDD, compounds that are environmentally important	U.S. Department of Health and Human Services

Table 5-15. Ongoing Studies on Environmental Fate and Treatment of CDDs (continued)

Investigator	Affiliation	Title	Sponsor
Zauderer B	Coal Tech Corp Merion Station, PA	Control of Dioxin Emissions from Waste Fuel Combustion by Cofiring with Coal	U.S. Department of Energy
Zimbeck W	Technology Assessment & Transfer, Inc. Annapolis, MD	Experimental Evaluation and Scientific Study of Treatment Technologies for Dioxin Contaminated Soil	U.S. Air Force
Not identified	Xenobiotic Detection Systems, Inc., Durham, NC	Validation of Serum Bioassay for Dioxin-like Toxicants	U.S. Department of Health and Human Services HHS
Not identified	Hybrizyme Corp. Raleigh, NC	New Test Method for Dioxins in Human and Animal Samples	
Not identified	A. Ahlstroem Osakeyhtioe, Karhula, Finland	Processing and Flue Gases and Ashes from CFB Combustion of Municipal Waste to Control Dioxine Concentrations	Ministry of Trade and Industry, Helsinki (Finland)
Not identified	Kuopio University, Department of Environmental Sciences Kuopio, Finland	Release of Chlorinated Hydrocardons in Refuse Incineration	Imatran Voiman Saeaetioe, Helsinki (Finland)
Not identified	Technical Research Centre of Finland, Combustion and Thermal Engineering Lab Jyvaeskylae (Finland)	Emissions from Fluidized Bed Combustion of Waste	Ministry of Trade and Industry, Helsinki (Finland)
Not identified	Kuopion University, Department of Environmental Sciences Kuopion University	Formation of Chlorinated Hydrocarbons in Combustion of Waste Materials	Ministry of Trade and Industry, Helsinki (Finland)
Not identified	AEA Technology	Coalite Works: Soil Survey and Emission Monitoring	Her Majesty's Inspectorate of Pollution
Not identified	Environmental Protection Agency (EPA), Acurex Environmental Corporation, Research Triangle Park, NC	The Effect of Coal Sulfur on Dioxin Formation	

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL SAMPLES

The primary method of determining CDDs in biological samples is gas chromatography (GC) with mass spectrometry (MS). Sample preparation is critical, and extensive extraction and sample clean-up are required to separate the CDD homologues/congeners from fatty material and other organic contaminants. Extreme care must also be used to ensure that all reagents and equipment used in analysis are free of CDD contamination. Losses of CDDs can occur as a result of adsorption onto the surfaces of glassware used in sample preparation (EPA 1994c). The routine baking of glassware as a part of the cleaning process should be avoided because this may cause active sites on the glass that will irreversibly adsorb CDDs. The lack of interferences must be demonstrated under the conditions of analysis. Analysts should avoid polyvinyl chloride (PVC) gloves (EPA 1994c). The basic steps of sample preparation include extraction of the sample with a lipophilic organic solvent (e.g., hexane) followed by several evaporation and column chromatography steps to concentrate, clean up, and fractionate the CDDs.

Methods of measuring CDDs in biological samples are very sensitive, generally having method (sample matrix) detection limits in the low- or sub-parts per trillion (ppt) level. If rigorous sample preparation methods are meticulously followed, sensitivity, accuracy, selectivity, and precision can be good. These parameters will vary with the analytical method used, the experience level of the technician, the nature of the sample matrix, the concentrations of the analyte(s) and possible interfering substances, and the specific

homologue/congener being measured. High-resolution gas chromatography (HRGC) is used almost exclusively. The MS method may be low resolution (LRMS), high resolution (HRMS), or tandem LRMS (MS/MS). Individual ionization techniques that have been commonly used with MS to determine CDDs include electron impact ionization (EI), chemical ionization (CI), and negative chemical ionization (NCI). Electron impact ionization instruments are the most common although the least sensitive. The use of CI and NCI methods can improve instrumental sensitivity because less molecular fragmentation occurs, with the resulting ion current concentrated in fewer ions compared to EI. NCI is very selective for those compounds that tend to capture electrons and form negative ions. Both CI and NCI can greatly increase selectivity and sensitivity in complicated matrices. Selected ion monitoring (SIM) is most frequently used for quantitation; however, multiple ion monitoring (MIM), also called multiple ion detection (MID), has also been employed. Isotopically labeled internal standards (such as ^{13}C- or ^{37}Cl-labeled CDDs) are needed both for quantitation and to monitor method performance. Table 6-1 is a summary of some of the most commonly used methods for detecting CDDs in biological samples. Many of the methods for food and wildlife (Table 6-2) could have applicability to CDDs in human samples of similar composition.

HRGC combined with HRMS has been used to determine parts per quadrillion (ppq) levels of CDDs in blood, serum, and plasma (Chang et al. 1993; Nygren et al. 1988; Patterson et al. 1987a, 1989b). Method 8290 (EPA 1994c) is applicable to adipose tissue with a limit of detection of 1 ppt. Method 8290 has also been used to determine CDDs in blood and semen (Schecter 1996). The methods differ in the solvent system used to extract the dioxins and the types of columns used to clean up and fractionate the samples. The method of Chang et al. (1993) used solid phase extraction for the initial step of the isolation. Detection limits were comparable for CDD, but the method used by Patterson et al. (1987a) gave better recovery of the analyte. Precision was similar, with a coefficient of variation (CV) that ranged from 2 to 22% for TCDD.

2,3,7,8-TCDD has been detected (sub-ppt) in human feces using HRGC/LRMS (Wendling et al. 1990). In rodent metabolism studies both parent compound and metabolite were detected in feces and metabolites were detected in urine using GC/LRMS. HRGC/LRMS has also been used successfully in determination of CDDs in rat feces (Abraham et al. 1989a). Adequate comparisons of sensitivity, accuracy, and precision cannot be made because of the lack of these data for several methods and the differences in the media and analytes for the available data.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human serum (CDDs)	Addition of ^{13}C-labeled CDD/CDF mixture to sample; extraction with $(NH_4)_2SO_4$, ethanol, and hexane; washing of hexane layer with distilled water; volume reduction; clean-up with column chromatography	HRGC/HRMS (EI, NCI)	6–150 ppq	No data	Patterson et al. 1989b (CDC method)
Human serum (CDDs)	Addition of ^{13}C-labeled CDD/CDF mixture to sample; extraction with sequential addition of potassium oxalate, ethanol ether, and pentane; remove and washing of pentane layer; clean-up using column chromatography	HRGC/HRMS (EI, NCI)	6–150 ppq	No data	Patterson et al. 1989b
Human serum (2,3,7,8-TCDD)	Addition of [^{13}C]2,3,7,8-TCDD to sample; extraction with $(NH_4)_2SO_4$, ethanol, and hexane; removal of hexane layer and washing with H_2SO_4 and deionized water; volume reduction; clean-up with column chromatography	HRGC/HRMS (SIM)	5 ppq	90–113	Patterson et al. 1987a
Blood (CDDs)	Addition of ^{13}C-labeled CDDs to 100 mL of sample followed by addition of formic acid, equilibration and degassing; passage through C_{18} SPE, elution with hexane and volume reduction; fractionation using benzene sulfonic acid SPE, silica SPE, and Florisil; volume reduction.	HRGC/HRMS (SIM)	<0.005 ng/kg (0.005 ppt)	70–80 at 50 ppq (41% for OCDD)	Chang et al. 1993
Human plasma (CDDs)	Extraction with methanol/chloroform, followed by chloroform/water; removal of chloroform layer and washing with water; evaporation; redissolution in hexane; clean-up on silica gel, elution with hexane; addition of tetradecane and evaporation; redissolution in hexane; separation on Carbopack C®/Celite 545®, elution with toluene; addition of tetradecane followed by solvent evaporation; redissolution in toluene containing ^{13}C-labeled internal standard	HRGC/HRMS (EI/MIM)	3–20 ppq	65–121 (TCDD); 64–135 (CDDs)	Nygren et al. 1988

Table 6-1. Analytical Methods for Determining CDDs in Biological Materials (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rat urine and feces (CDD metabolites)	Homogenization of fecal samples with distilled water; acidifcation of both urine and fecal samples with H_2SO_4 followed by extraction with toluene; centrifugation of fecal sample and removal of aqueous layer; removal of water from extracts with $MgSO_4$ followed by solvent evaporation; redissolution in acetone; methylation with methyl iodide/K_2CO_3; centrifugation to remove excess K_2CO_3; evaporation of acetone; redissolution in toluene; volume reduction; clean-up on silica gel plate using TLC; elution with toluene; volume reduction	GC/LRMS (EI/MIM)	No data	No data	Tulp and Hutzinger 1978
Rat feces (CDDs)	Grinding of sample with Na_2SO_4; addition $^{13}C_{12}$-labeled CDD/CDF mixture; Soxhlet extraction with toluene; volume reduction; clean-up on alumina column, elution with hexane; volume reduction; clean-up on silica gel, elution with hexane; volume reduction; clean-up on alumina B Super®, elution with hexane; solvent evaporation; redissolution in benzene	HRGC/LRMS (EI/MIM)	No data	75–95 (TCDD); >60 (CDD)	Abraham et al. 1989a
Human feces (2,3,7,8-TCDD)	Addition of [^{3}H]2,3,7,8-TCDD to sample; digestion with H_2SO_4; extraction with hexane; clean-up sequentially on silica gel, alumina, and Carbopack C/Celite®; addition of tribromobiphenyl	HRGC/LRMS (EI/SIM)	0.08–0.1 ppt	59–82	Wendling et al. 1990
Human adipose tissue (CDDs)	Addition of [^{37}Cl]2,3,7,8-TCDD to sample; hydrolysis with KOH, ethanol, and heat; extraction with petroleum ether; washing of organic layer with water and H_2SO_4; volume reduction; clean-up on silica gel; elution with hexane; clean-up on alumina; elution with CH_2Cl_2; volume reduction; redissolution in tridecane	HRGC/LRMS (EI/SIM)	10 ppt	No data	Schecter et al. 1985b

Table 6-1. Analytical Methods for Determining CDDs in Biological Materials (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human adipose tissue (CDDs)	Addition of isotope-labeled standards to sample; homogenization and extraction with CH_2Cl_2; clean-up with gel permeation chromatography; clean-up and fractionation on Carbopak® C/Celite® or Florisil®/AMOCO PX-21®	HRGC/MS (SIM)	1 ppb	50–90	Stanley 1986 (EPA method)
Human adipose tissue (CDDs)	Clean-up of sample on potassium silicate/silica gel column, elution with cyclohexane/CH_2Cl_2; clean-up on carbon column, elution with toluene; clean-up sequentially on potassium silicate column in tandem with alumina column, elution with hexane followed by CH_2Cl_2 in hexane	HRGC/HRMS (EI/MIM)	No data	No data	Nygren et al. 1988
Human adipose	Addition of ^{13}C-labeled standards to tissue followed by extraction with methylene chloride, acid-base washing, solvent exchange, treatment with silica gel impregnated with sulfuric acid, column chromatography using acidic silica gel, neutral alumina, and activated carbon; addition of ^{13}C-labeled standards.	HRGC/HRMS (EPA Method 8290)	1 ppt	No data	EPA 1994c
Human lung, liver, kidney, and adipose tissue (CDDs)	Homogenization of sample; saponification with KOH/ethanol; washing with H_2SO_4 and water; extraction with hexane/acetonitrile; clean-up on alumina column, elution with hexane/CH_2Cl_2; addition of [^{13}C]1,2,3,4-TCDD	HRGC/LRMS (SIM)	10 ppt	35–115	Takizawa and Muto 1987
Human adipose, liver, and kidney tissue (CDDs)	Homogenization of tissue; extraction with acetone/hexane,removal of fat with H_2SO_4; clean-up on Florisil® and activated carbon	HRGC/MS/MS (CI)	2 ppt	No data	Ryan et al. 1987a
Human adipose tissue	Homogenization of tissue; extraction on column via elution with cyclohexane/CH_2Cl_2; clean-up with hexane and H_2SO4; re-extraction with pentane/cyclohexane; clean-up on alumina, Florisil®, and silica:carbon column	HRGC/MS	0.2 ppb	86–100	Wagner et al. 1991

Table 6-1. Analytical Methods for Determining CDDs in Biological Materials (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rat liver and adipose tissue; rat fetuses (CDDs)	Grinding of sample with Na_2SO_4; addition of [^{13}C]2,3,7,8-TCDD and OCDD; Soxhlet extraction with toluene; volume reduction; addition of hexane; clean-up with column chromatography	HRGC/LRMS (SIM)	No data	No data	Van den Berg et al. 1987b
Rat liver tissue (CDDs)	Grinding of sample with Na_2SO_4; addition of [^{13}C]2,3,7,8-TCDD and OCDD; Soxhlet extraction with toluene; volume reduction; addition of hexane; clean-up with column chromatography	HRGC/LRMS (EI/SIM)	100–250 pg	No data	Van den Berg et al. 1989
Human milk (CDDs)	Centrifugation of sample to separate aqueous and lipid fractions; mixing of lipid layer with Na_2SO_4 and washing with hexane; addition of [^{13}C]2,3,7,8-TCDD and [^{13}C]OCDD; shaking with H_2SO_4 and silica; filtration and collection of hexane layer; addition of nonane and volume reduction; clean-up on Super-Macro™, Macro™, and High Aspect™ columns; fractionation on Zorbax™ octadecylsulphate column using HPLC	HRGC/LRMS (SIM)	0.05–50 ppt	No data	Van den Berg et al. 1986b
Human milk (CDDs)	Mixing of sample with formic acid and Lipidex 5000®; transfer of gel mixture into column and elution with acetonitrile; evaporation of solvent; redissolution in hexane; clean-up on aluminum oxide column, elution with hexane; clean-up on silica gel, elution with hexane; clean-up on aluminum oxide, elution with CH_2Cl_2 in hexane; volume reduction	HRGC/HRMS (SIM)	No data	79–91	Noren and Sjoevall 1987

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; CH_2Cl_2 = dichloromethane (methylene chloride); CI = chemical ionization; EI = electron impact; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; HRMS = high-resolution mass spectrometry; H_2SO_4 = sulfuric acid; K_2CO_3 = potassium carbonate; KOH = potassium hydroxide; LRMS = low-resolution mass spectrometry; $MgSO_4$ = magnesium sulfate; MIM = multiple ion monitoring; MS = mass spectrometry; Na_2SO_4 = sodium sulfate; NCI = negative chemical ionization; $(NH_4)_2SO_4$ = ammonium sulfate; OCDD = 1,2,3,4,5,6,7,8-OCDD = octachlorodibenzo-*p*-dioxin; ppb = parts per billion; ppq = parts per quadrillion; ppt = parts per trillion; SIM = selective ion monitoring; 2,3,7,8-TCDD = tetrachlorodibenzo-*p*-dioxin; TLC = thin layer chromatography

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (hazardous waste site) (2,3,7,8-TCDD)	Collection of sample onto glass fiber filter/polyurethane foam cartridge; add [$^{37}Cl_4$]2,3,7,8-TCDD and [$^{13}C_{12}$]2,3,7,8-TCDD; Soxhlet extraction with CH_2Cl_2; clean-up with acid/base sequentially on silica gel, modified silica gel, alumina, and carbon	HRGC/LRMS	No data 0.02 pg/m^3	91–112 74–112	Fairless et al. 1987 Harless et al. 1992
Air (CDDs)	Drawing of approximately 325 m^3 of air through quartz fiber filter/polyurethane foam; Soxhlet extraction with benzene, volume reduction; clean-up using silica, alumina, activated carbon; volume reduction; addition of [$^{13}C_{12}$]2,3,7,8-TCDD.	HRGC/HRMS; MID (EPA TO-9)	1–5 pg/m^3	68–140 from ultrapure, filtered air	EPA 1988g
Air (CDDs)	Collection of sample onto glass fiber filter/polyurethane foam cartridge; addition of internal standard; Soxhlet extraction with toluene; volume reduction; clean-up and fractionation on Florisil®, elutiion with toluene/diethylether, evaporation and redissollution in cyclohexane; clean-up on modified silica gel using HPLC and hexane/diethyl ether; volume reduction	HRGC/LRMS (EI/SIM); HRGC/LRMS (NCI/SIM)	0.1–1 pg/m^3 0.2–3 pg/inj (0.01–0.1 pg/m^3)	80–122 86–102	Oehme et al. 1986
Air (CDDs)	Collection of sample onto quartz fiber/polyurethane foam plug; Soxhlet extraction with acetone; clean-up with hexane and sulfuric acid followed by silica gel and alumina columns	HRGC/MS (SIM)	0.5 pg/m^3	70–90	Kuwata et al. 1993
Air (CDDs)	Collection of sample onto glass fiber filter/XAD-2® cartridge with $^{13}C_{12}$- labeled CDD mixture added; Soxhlet extraction with toluene and tetradecane; evaporation and redissolution in hexane; clean-up on silica, elution with hexane; evaporation and redissolution in hexane; clean-up on Carbopack C®/Celite 545®, elution with toluene	HRGC/LRMS (EI)	0.01–0.05 pg/m^3	≤5	Rappe et al. 1988

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Standards	Coating wells of microtiter plate with TrCDD-hapten-protein conjugate; blocking with ovalbumin; solubilization of CDD or other test compound in BSA using ultrasonication; application of test compound to wells of microtiter plate; addition of hybidoma antibody and incubation; washing with Tween 20®/water; addition of peroxidase-conjugated goat anti-mouse antiserum; addition of 2,2-azino-di-3-ethyl benzthazoline sulfonic acid	ELISA/UV	0.5 ng	No data	Stanker et al. 1987
Drinking water (CDDs)	Addition of ^{13}C-labeled CDD internal standards; extraction with organic solvent; volume reduction; clean-up on multiple columns of silica gel/basic silica/acidic silica, $AgNO_3$-silica/basic alumina, and HPLC	HRGC/LRMS (SIM); HRGC/MS/MS (SIM)	No data	No data	McCurvin et al. 1989
Drinking water (CDDs)	Filtration of sample and collection of CDDs on Separalyte™ cartridge using HPLC; elution from cartridge with acetone; solvent exchange with hexane; water removal using Na_2SO_4; concentration and exchange with benzene; Soxhlet extraction of filters with benzene and addition to cartridge extract; volume reduction; sequential clean-up on acid alumina, graphitized carbon on Celite 545®, and neutral alumina columns	HRGC/LRMS (SIM)	0.5–1.1 ppq	86–124	O'Keefe et al. 1986
Fog (water and particulates) (CDDs)	Collection of sample on Teflon® screen collector; extraction with CH_2Cl_2; solvent evaporation and redissolution in hexane; clean-up on silica gel column, elution with CH_2Cl_2; clean-up on alumina column, elution with hexane/CH_2Cl_2; volume reduction; addition of ^{13}C-labeled CDD/CDF standards	HRGC/HRMS (MIM)	No data	No data	Czuczwa et al. 1989

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Landfill leachate (oil extract and bottom layer) (CDDs)	Homogenization of oil sample and dissolution in benzene; addition of ^{13}C-labeled CDD standards; homogenization of bottom sample and dissolution in toluene; addition of ^{13}C-labeled CDD standards followed by reflux and filtration; volume reduction and addition to benzene; for both sample types, clean-up on alumina/Na_2SO_4 column, elution with hexane/CH_2Cl_2; volume reduction; clean-up on silica gel/H_2SO_4/Na_2SO_4 column, elution with hexane; volume reduction; clean-up on Bio-Beads S-X3® column, elution with cyclohexane/ethylacetate; solvent evaporation; redissolution in benzene; clean-up on alumina/Na_2SO_4 column, elution with hexane/CH_2Cl_2; addition of [$^{13}C_6$]1,2,3,4-TCDD; volume reduction	HRGC/LRMS (MIM)	0.02 ppb	60–80	Först et al. 1988
Groundwater, soil, sediment (HxCDD, HpCDD, OCDD)	Extraction of soil and sediment samples with Na_2SO_4/acetonitrile/CH_2Cl_2; centrifugation; removal of organic supernatant and filtration into sampling vial; extraction of water samples with CH_2Cl_2; washing with KOH and water removal with Na_2SO_4; vlume reduction	HRGC/LRMS (CI/SIM); HRGC/MS/MS	No data No data	No data No data	Pereira et al. 1985
	Mixing of sediment with Na_2SO_4, oven drying overnight, and soxhlet extraction with hexane:acetone (1:1) for 16 hours; washing of extract with saturated NaCl, solvent volume reduction, sulfur removal, column clen-up, solvent exchange to DMSO; Extraction of water with hexane and solvent exchange to DMSO.	Chemical-Activated Luciferase Gene Expression (CALUX)	<1 pM per well (<0.5 fmol/well; 32 fg/well)	No data	Murk et al. 1996
Water, soil (2,3,7,8-TCDD equivalents)	Details for sample preparation were not reported by the authors.	Enzyme induction assay (EROD)	62.5 pg/L	No data	Schuman and Hunter 1988
Water, soil, sediment, fly ash, fuel oil, sludge, still bottoms, fish, adipose	Addition of ^{13}C-labeled standards followed by solvent extraction (exact method depends on matrix), acid-base washing treatment, solvent exchange, and cleanup using alumina, silica gel, and activated carbon, addition of ^{13}C-labeled internal standards.	HRGC/HRMS (MIM); (EPA Method 8290)	10 ppq for water to 1 ppt for other matrices (depending on complexity)	No data	EPA 1994c

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil, sediment (CDDs)	Addition of isotopically labeled internal standards to sample; addition of Na_2SO_4 and extraction with hexane/methanol or Soxhlet extraction with toluene; clean-up using column chromatography if needed; volume reduction	HRGC/MS (EI/SIM)	No data	No data	Eschenroeder et al. 1986
Soil, sediment (2,3,7,8-TCDD)	Soxhlet extraction of sample; volume reduction; clean-up on basic silica/acidic, silica/alumina, elution with CH_2Cl_2 in hexane; analysis; clean-up on silver nitrate silica or 2,3,7,8-TCDD-specific alumina, elution with CH_2Cl_2 in hexane; analysis; repeating of clean-up or extraction if needed	HRGC/LRMS (SIM); HRGC/MS/MS (SIM)	1 ng/g <1 ng/g	40–90 57–102	Simon et al. 1989
Soil, sediment (CDDs)	Mixing of Na_2SO_4 and sample; elution with acetone/ethyl acetate/CH_2Cl_2; evaporation and redissolution in hexane	HRGC/ECD	No data	92–100	Jasinski 1989
Soil (CDDs)	Sieving of sample; addition of [$^{13}C_{12}$]2,3,7,8-TCDD and [$^{13}C_{12}$]1,2,3,4,6,7,8-HpCDD; Soxhlet extraction with hexane/acetone; removal of organic layer and clean-up on Na_2SO_4/H_2SO_4/silica/$NaHCO_3$; volume reduction of eluate and clean-up on Florisil®, elution with CH_2Cl_2; volume reduction; addition of dodecane and hexane; clean-up on porous graphite column using HPLC and elution with hexane; addition of dodecane and volume reduction	HRGC/MS (SIM)	1 ng/kg	53–86	Creaser and Al-Haddad 1989
Soil (CDDs)	Soxhlet extraction with toluene; addition of [$^{13}C_{12}$]2,3,7,8-TCDD and [$^{13}C_{12}$]OCDD; volume reduction; clean-up on silica and alumina columns	GC/MS/MS GC/LRMS GC/HRMS	2–38 pg 5–20 pg 1–5 pg	No data	Bobbie et al. 1989
Soil (from hazardous waste site) (CDDs)	Addition of [^{13}C]-2,3,7,8TCDF and OCDD and [^{37}Cl]2,3,7,8-TCDD; extraction and clean-up using column chromatography	HRGC/LRMS (EI/SIM)	No data	No data	Stalling et al. 1986

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil, fly ash, pottery clay, still bottoms, sludges (CDDs)	Addition of [$^{13}C_{12}$]2,3,7,8-TCDD to sample and, if not a soil sample, extraction as in EPA method 8280; if soil sample, addition of Na_2SO_4 and extraction with petroleum ether and methanol; filtration of soil sample extract into Kuderna-Danish concentrator and addition of petroleum ether; volume reduction, addition of hexane, and volume reduction again; washing of all extracts (soil, chemical waste, etc.) sequentially with KOH, distilled water, H_2SO_4, and distilled water; clean-up on alumina, elution with CH_2Cl_2 in hexane; volume reduction, addition of isooctane during evaporation; just prior to analysis, dilution with isooctane or tridecane; if extra clean-up is necessary, use of HPLC	HRGC/LRMS (SIM) HRGC/ECD	3 ng/g (solid samples); 3 ng/L (liquid samples) No data	60–96 (soil); 62–90 (pottery clay); 68–104 (still bottom) 40–106 (pottery clay)	Donnelly et al. 1986 (modified EPA method 8280)
Soil, water, still bottoms, fuel oils, sludges, fly ash, reactor residues (CDDs, CDFs)	Addition of [$^{13}C_{12}$]CDDs and [$^{13}C_{12}$]CDFs followed by extraction (matrix specific); washing with 20% KOH, 5% NaCl, concentrated sulfuric acid, 5% NaCl, water removal, solvent exchange, and fractionation on alumina; collection of fraction eluted by 60% methylene chloride/hexane; clean-up on carbon column; addition of [$^{13}C_{12}$]1,2,3,4-TCDD.	HRGC/LRMS; MID (EPA 8280)	2 ppb (soils), 10 ppb (other solid wastes), 10 ppt (water)	54–125 (depends on matrix, isomer)	EPA 1986k
Water, soil, sediment, sludge, fish, tissues (tetra- through octa-CDDs and CDFs)	Addition of ^{13}C analogs of 15 of the 2,3,7,8-CDDs/CDFs to sample; filtration, homogenization, acid digestion (depending on matrix) followed by SPE for water samples and liquid/liquid extraction for others; addition of [$^{37}Cl_4$]2,3,7,8-TCDD and clean-up using back extraction with acid and/or base, gel permeation, alumina, silica gel, Florisil, and activated carbon, depending on matrix; volume reduction; addition of internal standard	HRGC/HRMS (EPA 1613)	4 ppq for 2,3,7,8-TCDD in water; 1 ppt in solid	25–164	EPA 1994a
Foods (CDDs)	Homogenization of sample; saponification with KOH/ethanol; washing with H_2SO_4 and water; extraction with hexane/acetonitrile clean-up on alumina column, elution with hexane/CH_2Cl_2; addition of [^{13}C]1,2,3,4-TCDD	HRGC/LRMS (SIM)	10 ppt	35–115	Takizawa and Muto 1987

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Foods (CDDs)	Homogenization of sample, addition of 1,3,7,8-TCDD, and digestion with KOH/ethanol solution; extraction with hexane; washing of organic phase with water and H_2SO_4; clean-up on acid-silica column/Florisil® column, elution with hexane followed by CH_2Cl_2; evaporation and redissolution in acetonitrile-CH_2Cl_2; clean-up using HPLC	HRGC/ECD	No data	85–106	Jasinski 1989
Beef fat CDDs, CDFs)	Addition of ^{13}C analogs of 15 of the 2,3,7,8-CDDs/CDFs to sample; filtration, homogenization, acid digestion (depending on matrix) followed by SPE for water samples and liquid/liquid extraction for others; addition of $^{37}Cl_4$-2,3,7,8-TCDD and clean-up using back extraction with acid and/or base, gel permeation, BioSil, PX-21 carbon cleanup; volume reduction; addition of internal standard	HRGC/HRMS (Modification of EPA 1613)	0.05 ppt (wt:wt) for TCDD	56-96 (±20%)	Ferrario et al. 1996
Crab tissue (CDDs, CDFs)	Addition of ^{13}C-labeled standards, digestion with 30% ethanolic KOH; extraction with hexane; washing with sulfuric acid; column chromatography using silica gel, neutral alumina, activated carbon/silica; volume reduction	HRGC/HRMS (MID)	3–15 ppt	40–110	Cai et al. 1994
Fish (CDDs, CDFs)	Blending of sample with anhydrous sodium sulfate, addition of ^{13}C-labeled standards followed by Soxhlet extraction with hexane/methylene chloride (1:1); volume reduction and sovent exchange to isooctane; columen chromatography on silica gel/potassium silicate/sodium sulfate/celite/sulfuric acid/sodium sulfate; volume reduction and solvent exchange to isooctane; clean-up using Florisil, carbon/silica; volume reduction and addition of internal standard	HRGC/HRMS (MID)	1 ppt (2,3,7,8-TCDD)	94–109	Marquis et al. 1994
Fish tissue (CDDs)	Homogenization of sample; digestion with HCl; extraction with hexane; clean-up on glass column containing H_2SO_4; addition of [$^{13}C_{12}$]2,3,7,8-TCDD, [$^{13}C_{12}$]OCDD, and 2,3,7,8-TCDD; volume reduction; clean-up on silica and alumina columns; clean-up with HPLC	HRGC/MS/MS HRGC/LRMS HRGC/HRMS	2–38 pg 5–20 pg 1–5 pg	85–12,500 105–110 ND–95	Bobbie et al. 1989

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish (2,3,7,8-TCDD equivalents)	Homogenization of sample; digestion with HCl; extraction with pentane; filtration of pentane extract through Na_2SO_4; evaporation; redissolution with pentane/toluene and washing with H_2SO_4; removal of organic layer and clean-up on Na_2SO_4/basic silica gel/acidic silica gel column, elution with pentane; evaporation and redissolution in pentane; clean-up on Carbopak C®/Celite 545® column, elution with toluene; evaporation and redissolution in DMSO; addition to cells	Enzyme induction assays (EROD and AHH)	No data	No data	Zacharewski et al. 1989
Herring gull eggs (CDDs)	Homogenization of sample and extraction; clean-up on Biobeads SX-3® using gel permeation chromatography, elution with CH_2Cl_2/hexane; clean-up by sequential carbon, Florisil®, and alumina column chromatography	HRGC/LRMS (EI/SIM)	10 pg/g	No data	Stalling et al. 1986
Fish, birds, seals (CDDs)	No methods details; extraction and clean-up on silica, modified silica, and alumina columns used; internal standards added	HRGC/LRMS (EI/SIM)	1–50 pg	No data	Buser et al. 1985
		HRGC/LRMS (NCI/SIM)	0.01–0.1 pg		
Wipe and liquid samples from pyrolized transformer oil (CDDs)	Extraction with organic solvent and washing of organic layer sequentially with base and acid; separation on neutral silica gel; clean-up and fractionation on carbon/silica column	HRGC/LRMS	No data	83–134 (wipe); 19–70 (liquid)	Hardin et al. 1989
Wipe and liquid samples from pyrolized transformer oil (CDDs)	Extraction with organic solvent; clean-up on neutral silica/basic silica/acidic silica column; clean-up and fractionation by sequential chromatography on basic alumina, carbon/silica gel, and Sepralyte® columns	HRGC/HRMS	No data	58–151 (wipe) 51–136 (liquid)	Hardin et al. 1989 (ASME method)
Liquid and gaseous waste effluents (CDDs)	Collection of gaseous samples on XAD-2 cartridge followed by Soxhlet extraction with benzene; addition of internal standards to liquid samples; clean-up and sequential fractionation on basic silica gel/neutral silica gel/acidic silica gel columns and alumina column; addition of $[^{37}CL_4]$2,3,7,8-TCDD	HRGC/HRMS (MIM)	1–7.8 pg/m^3 (gases); No data (liquids)	94–101 (gases); No data (liquids)	Cooke et al. 1988

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
PCP (CDDs)	Fractionation of sample on Na_2SO_4/neutral alumina column, elutiion with benzeneand on basic alumina, elutiion with CH_2Cl_2-hexane; evaporation and redissolution in toluene	GC/LRMS GC/HRMS	No data No data	>90 >90	Singh et al. 1985
Dust and swab samples (HpCDD and OCDD)	Collection of swab samples on cyclohexane-soaked gauze; extraction with hexane; collection of dust into vials followed by homogenization and Soxhlet extraction with hexane; evaporation to dryness and redissolution in hexane; addition of KOH to both sample types followed by centrifugation; removal of aqueous phase and washing of organic layer with deionized water; water removal using Na_2SO_4 column, elution with hexane; evaporation of sample and redissolution in cyclohexane/CH_2Cl_2; clean-up on activated carbon/silica column using HPLC, elution with CH_2Cl_2/methanol/benzene and toluene; evaporation and redissolution in hexane; removal of aliquot of sample to be analyzed, evaporation, and redissolution in *n*-hexadecane	HRGC/ECD	0.2–4 µg/m^2	61–90	Korfmacher et al. 1985
Cigarettes, and cigarette smoke and ash (CDDs)	Collection of smoke on glass fiber filter/polyurethane foam/XAD-II® cartridges; washing of ash samples with H_2SO_4; Soxhlet extraction of all samples with benzene; volume reduction; addition of hexane and [$^{13}C_6$]1,2,3,4-TCDD; washing with H_2SO_4; volume reduction, addition of hexane; clean-up on alumina, elution with CH_2Cl_2 in hexane; volume reduction; clean-up on Zolbax SIL®, elution with hexane; volume reduction; addition of benzene	HRGC/LRMS (SIM)	0.5 pg/g (cigarettes, ash); 0.22 ng/m^3 (smoke)	No data	Muto and Takizawa 1989
Incinerator stack emission; air from contaminated building (CDDs)	Addition of ^{13}C-labeled TCDD to collection tube followed by collection of sample; addition of internal standards; Soxhlet extraction; clean-up and sequential fractionation on acidic silica/potassium, silicate/silica gel, acidic alumina, carbon, neutral alumina columns; volume reduction	HRGC/HRMS (MIM)	1 pg/m^3	No data	Smith et al. 1986b

Table 6-2. Analytical Methods for Determining CDDs in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Car exhaust (CDDs)	Addition of ^{13}C-labeled CDD standards to XAD-2® resin of an EPA MM5 sampling train; collection of sample; Soxhlet extraction with toluene; clean-up and fractionation on acid- and base-modified silica; further fractionation on basic alumina; clean-up on activated carbon; evaporation and redissolution in isooctane	HRGC/HRMS (EI, SIM)	No data	36–165	Bingham et al. 1989

$AgNO_3$ = silver nitrate; AHH = aryl hydrocarbon hydroxylase; ASME = American Society for Mechanical Engineering; BSA = bovine serum albumin; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; CH_2Cl_2 = dichloromethane (methylene chloride); CI = chemical ionization; DMSO = dimethylsulfoxide; ECD = electron capture detection; EI = electron impact; ELISA = enzyme-linked immunosorbant assay; EPA = Environmental Protection Agency; EROD = ethoxyresorufin O-deethylase; GC = gas chromatography; HCl = hydrochloric acid; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; HRMS = high-resolution mass spectrometry; H_2SO_4 = sulfuric acid; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzofuran; inj = injection; KOH = potassium hydroxide; LRMS = low-resolution mass spectrometry; MIM = multiple ion monitoring; MM5 = modified method 5; MS = mass spectrometry; $NaHCO_3$ = sodium bicarbonate; Na_2SO_4 = sodium sulfate; NCI = negative chemical ionization; OCDD = octachlorodibenzo-*p*-dioxin; PCP = pentachlorophenol; ppq = parts per quadrillion; SIM = selective ion monitoring; 2,3,7,8-TCDD = tetrachlorodibenzo-*p*-dioxin; 2,3,7,8-TCDF = tetrachlorodibenzofuran; TrCDD = trichlorodibenzo-*p*-dioxin; UV = ultraviolet detection

HRGC has been combined with LRMS, HRMS, and MS/MS for the detection of CDDs in tissues. Sensitivity is generally in the ppt range with the best sensitivity (2 ppt) reported with MS/MS using CI (Ryan et al. 1987a). The limit of detection was higher for MS than for MS/MS (Schecter et al. 1985b; Stanley 1986; Takizawa and Muto 1987). No recovery data were given for HRMS (Nygren et al. 1988). Precision for these methods is usually <20% (Takizawa and Muto 1987; Van den Berg et al. 1989).

CDDs have been measured in breast milk using HRGC/MS in the SIM mode. Reported detection limits are in the low- to sub-ppt (Van den Berg et al. 1986b), and recovery (75–89%) is good (Noren and Sjoevall 1987).

An additional screening test for TCDD-like (aryl hydrocarbon receptor, AhR, active) chemicals has been developed (Garrison et al. 1996) and is available commercially (Anonymous 1997). Dubbed the CALUX (for chemically activated luciferase gene expression) system, the assay is based on recombinant cell lines into which researchers have inserted a firefly luciferase gene. When exposed to dioxin-like compounds, the recombinant cells luminesce. The method is sensitive to ppt levels of 2,3,7,8-TCDD equivalents in blood, serum, and milk (Anonymous 1997). Samples testing positive can be subjected to more definitive and specific analytical testing.

6.2 ENVIRONMENTAL SAMPLES

As with biological samples, the most common method of determining CDDs in environmental samples is HRGC/HRMS. Other methods, including enzyme bioassays, and monoclonal antibody-based enzyme-linked immunosorbent assays (ELISAs) have also been used or are under development. Even in relatively simple matrices, such as air and water, detection and quantitation of CDDs require rigorous sample preparation procedures. Methods used to prepare environmental samples are similar to those used for biological samples: organic solvent extraction of CDDs from the sample and concentration, clean up, and fractionation of the dioxins using evaporative and column chromatography techniques. The same MS techniques described for biological samples are available for environmental samples, with essentially the same results and limitations. Table 6-2 describes some of the most common methods that have been used to determine CDDs in environmental samples, with specific MS techniques listed when known. The following section describes the methods available for the different types of environmental samples.

HRGC/LRMS and HRGC/HRMS have been used to analyze for CDDs in ambient and hazardous waste site air, cigarette smoke, car exhaust, and gaseous waste emissions. Sample preparation steps for gaseous samples are very similar for these two analytical methods. The steps consist of collection of sample contaminants on a filter/trapping cartridge apparatus, organic solvent extraction of the cartridge, and clean up and fractionation of the extract using column chromatography (Bingham et al. 1989; Cooke et al. 1988; Fairless et al. 1987; Harless et al. 1992; Muto and Takizawa 1989; Oehme et al. 1986; Rappe et al. 1988; Smith et al. 1986). A quartz fiber filter and polyurethane foam plug are commonly used to collect air samples (EPA 1988g; Harless et al. 1992; Kuwata et al. 1993), although XAD-2 has also been used (Hippelein et al. 1993). The sensitivity of these methods is in the low- to sub-pg/m^3 range. Reported recovery and precision were generally good for measurements in air and gaseous waste emissions (Cooke et al. 1988; Fairless et al. 1987; Oehme et al. 1986), but severe sample loss can occur (Bingham et al. 1989; Rappe et al. 1988). Electron capture, negative ionization, low resolution MS has also been used to quantify CDDs in ambient air; however, 2,3,7,8-TCDD is difficult to detect using this method and results must be confirmed with HRGC (Koester et al. 1992).

Methods have been developed for detecting CDDs in liquid samples including drinking water (McCurvin et al. 1989; O'Keefe et al. 1986), groundwater (EPA 1986k, 1994a, 1994c; Pereira et al. 1985), fog (Czuczwa et al. 1989), liquid waste effluents (Cooke et al. 1988), an oil extract of landfill leachate (Först et al. 1988), pentachlorophenol (Singh et al. 1985), fuel oils, still bottoms, and reactor residues (EPA 1986k, 1994a), and pyrolyzed transformer oil (Hardin et al. 1989). HRGC was combined with either LRMS, HRMS, or MS/MS in these methods. Not all methods reported on recovery, precision, and sensitivity, so it is difficult to compare these parameters. Based on the data available, sensitivities range from sub-ppq (O'Keefe et al. 1986) to low-ppt levels (Först et al. 1988). Recoveries were usually >60% (Först et al. 1988; O'Keefe et al. 1986), although some lower values were reported (Hardin et al. 1989).

HRGC/LRMS, HRGC/HRMS, HRGC/MS/MS, and HRGC/ECD have been used to analyze for CDDs in soils and/or sediments (Bobbie et al. 1989; Creaser and Al-Haddad 1989; Donnelly et al. 1986; EPA 1986k, 1994a, 1994c; Eschenroeder et al. 1986; Jasinski 1989; Pereira et al. 1985; Simon et al. 1989; Stalling et al. 1986), solid wastes (Donnelly et al. 1986; Först et al. 1988; Popp et al. 1997), and other solid materials (Donnelly et al. 1986; Hardin et al. 1989; Korfmacher et al. 1985; Muto and Takizawa 1989). Detection limits for the MS methods range from low-ppt to low-ppb levels. The sensitivity cannot be compared to ECD because no detection limits were reported for the ECD methods. For soil/sediments, recovery seemed to be better for GC/ECD (92–100%) (Jasinski 1989) than for the HRGC/MS methods

(40–102%) (Creaser and Al-Haddad 1989; Donnelly et al. 1986; Simon et al. 1989). Polychlorinated biphenyls, polychlorinated diphenyl ethers, polychlorinated naphthalenes, and polychlorinated alkydibenzofurans may be found at concentrations several orders of magnitude higher than the analytes of interest (EPA 1994a) and could thus interfere with the CDDs. Retention times must be verified using reference standards.

A method for determining CDDs in municipal incinerator fly ash has been reported (Alexandrou and Pawliszyn 1990). The method uses supercritical fluid extraction (SFE) to recover CDDs from fly ash samples prior to GC. Supercritical fluid extraction is faster and less expensive than the typically used Soxhlet extraction and gives quantitative removal of CDDs and CDFs from fly ash. Extracts obtained using SFE will still require additional clean-up steps prior to analysis. Supercritical CO_2 has also been used to assist solvent-based extraction of CDDs from soils (Friedrich and Kleiböhmer 1997). In this case, the supercritical fluid was combined with accelerated solvent extraction (liquid extractions conducted under elevated temperature and pressure) to provide good recoveries relative to Soxhlet extractions.

TCDD and other CDDs have been measured in foods (Jasinski 1989; Schecter et al. 1994; Takizawa and Muto 1987) and wildlife (birds and bird eggs, fish, and seals) (Bobbie et al. 1989; Buser et al. 1985; EPA 1994a; Stalling et al. 1986) using HRGC/ECD or HRGC/LRMS. Schecter et al. (1994) reported data as TCDD toxic equivalents with detection limits of approximately 0.01 ppt. Ferrario et al. (1996) reported a new modification of EPA Method 1613 (EPA 1994a) for use in measuring CDDs and CDFs in beef fat; an LOD of 0.05 ppt was shown. A comparison of HRGC/LRMS methods conducted using samples from fish, birds, and seals showed that NCI was substantially more sensitive than EI for some, but not all, congeners (Buser et al. 1985). A within-lab comparison of fish tissue analysis using HRGC combined with either LRMS, HRMS, or MS/MS showed HRMS to be the most sensitive of the three methods (Bobbie et al. 1989). However, the large variations in recovery obtained with these methods also demonstrated the significance of the problems of sample loss and sample contamination that can occur in the analyses of CDDs. The data were not sufficient to permit a comparison of methods among different laboratories.

Bioassays using induction of the enzymes ethoxyresorufin *o*-deethylase (EROD) and/or arylhydrocarbon hydroxylase (AHH) in rat hepatoma H-4-IIE cells (Zacharewski et al. 1989) and modified mouse liver cells (Schuman and Hunter 1988) have been developed and tested on water, soil, and fish samples. The bioassays are based on induction of AHH or EROD enzymatic activity in the cell cultures. Since the cells used in the bioassays are most sensitive to induction by 2,3,7,8-TCDD, this dioxin is used to generate a

standard curve for the bioassays, and induction of activity is expressed as TCDD equivalents. These bioassays are highly sensitive to concentrations of Ah receptor-mediated cytochrome P-450 inducers (Holcomb et al. 1988; Zacharewski et al. 1989), and could be used to rapidly pre-screen environmental samples for 2,3,7,8-TCDD toxicity equivalents. A major drawback to these assays is that they are not highly selective. A number of halogenated aromatics other than CDDs can induce AHH and EROD activity (e.g., chlorinated dibenzofurans, polychlorinated biphenyls, and polychlorinated phenols), although none to the extent of TCDD induction. There is also a question about the possible effects of chemical mixtures, such as might be found in contaminated soil or fish, on the assay results (Zacharewski et al. 1989). An ELISA based on derivation of monoclonal antibodies specific to CDDs has also been investigated as a means of screening environmental samples for chlorinated dioxins (Stanker et al. 1987). Monoclonal antibodies (MAbs) developed using 1-amino-substituted 3,7,8-TrCDD derivatives could detect sub-ng levels of TCDD standards. The derived antibodies had a stronger affinity for CDDs substituted at the 1 position and for CDFs substituted at the 2, 3, 7, and 8 positions than for other CDDs including 2,3,7,8-TCDD. However, development of MAbs more specific for CDDs, especially 2,3,7,8-TCDD would provide a rapid, inexpensive, sensitive, and reasonably selective method for screening samples for CDD contamination. Sugawara and coworkers (Sugawara et al. 1998) have recently described an ELISA-based method for polychlorinated dibenzo-p-dioxins that can detect as little as 0.5 pg/well of 2,3,7,8-TCDD and shows great promise as a screening tool. The cross reactivity for octachloro-dibenzo-p-dioxin is very low (<0.1%), but it is much higher for compounds with three, four, or five chlorine atoms in a substitution pattern similar to the of 2,3,7,8-TCDD. As with all screening approaches, more accurate chemical analysis would be needed to confirm the compounds present.

The CALUX assay described in Section 6.1 has been applied to Ah receptor-active compounds (not limited to dioxins) in sediments and pore waters (Murk et al. 1996) and to blood with mixed results. Sensitivities as low as 0.5 fmol of 2,3,7,8-TCDD were reported. Two polychlorinated terphenyl mixtures, the PCB-substituted Ugilec 141, polybrominated diphenyl ethers, and the PCB mixture Clophen 150 were tested in the CALUX assay and had induction potencies that were 10^{-4} to 10^{-7} compared to TCDD. Thus, this assay is more selective than earlier, induction-based assays, although clearly not as selective as GC/MS.

6.3 ADEQUACY OF THE DATABASE

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

information on the health effects of CDDs is available. Where adequate information is not available, ATSDR, in conjunction with the 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 CDDs.

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods exist for determining CDDs in human serum and plasma, feces, biological tissues, and milk (Abraham et al. 1989a; Anonymous 1997; Chang et al. 1993; EPA 1994a, 1994c; Noren and Sjoevall 1987; Nygren et al. 1988; Patterson et al. 1987a, 1987b; Ryan et al. 1987a; Schecter et al. 1985b; Stanley 1986; Takizawa and Muto 1987; Van den Berg et al. 1989; Wendling et al. 1990). These methods have been used to determine ppq to ppt levels of CDDs in biological samples. The commonly used methods are sensitive enough to detect background levels of CDDs in most media, especially adipose tissue. The background concentration for non-occupationally-exposed people has been reported to be on the order of 4 ppt in lipid (Michalek et al. 1998). Improved clean-up and instrument sensitivity could make blood a more useful monitoring medium, although it is usually reagent and background contamination that is most problematic; CDD concentrations in blood tend be quite low. Improvements in current methods or development of new methods to increase sensitivity and selectivity would help to decrease the time involved in sample preparation, and would reduce the high cost ($800–$1,000 per sample) and possible errors associated with current methods of determining exposure to CDDs.

Several effects such as chloracne and alterations in hepatic metabolism have been associated with exposure to 2,3,7,8-TCDD in humans. However, these effects are not specific for 2,3,7,8-TCDD or other CDDs, but may be induced by numerous other chlorinated hydrocarbons. Determination of specific biomarkers of effect for CDD and development of reliable methods to quantify these effects would be useful in assessing the effects associated with exposure to CDDs.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods exist for measuring CDDs in a variety of environmental media, including air, water, sediment, soil, chemical waste, foods, fish, and other solid matrices (Bingham et al. 1989; Bobbie et al. 1989; Buser et al. 1985; Cai et al. 1994; Cooke et al. 1988; Creaser and Al-Haddad 1989; Donnelly et al. 1986; EPA 1986k, 1988g, 1994a, 1994c; Fairless et al. 1987; Jasinski 1989; Marquis et al. 1994; McCurvin et al. 1989; Muto and Takizawa 1989; Oehme et al. 1986; O'Keefe et al. 1986; Pereira et al. 1985; Rappe et al. 1988; Smith et al. 1986a). Of the EPA methods, Method 8280 (EPA 1986k) and 8290 (EPA 1994a) are both commonly used; Method 8290 is approximately three orders of magnitude more sensitive. Assuming an acute oral MRL of 20 pg/kg/day, an intermediate oral MRL of 7 pg/kg/day, and a 70-kg individual, the limit of detection needed for water (2 L/day consumption) is 770 ppq for acute and 245 ppq for intermediate exposure. The methods of O'Keefe et al. (1986) (LOD reported to be 0.5–1.1 ppq) and EPA (1994a, 1994c) (LODs reported to be 4 ppq to 10 ppq) are adequate for detecting CDDs in drinking water. If a 2 kg/day consumption of food is assumed, the needed method LODs will be 700 ppq for acute and 245 ppq for intermediate exposure. Of those method reporting LODs in foods, the methods of Bobbie et al. (1989) and of Ferrario et al. (1996) have the required LODs. Since CDDs are typically determined on a fat weight basis, the method of Ferrario et al. (1996) should be suitable for most food types once the fat is extracted. The sensitivity of the HRGC/MS methods is excellent, but because of the very low levels of these chemicals in the environment, increased sensitivity may be desirable in order to obtain detectable values. Increased accuracy and selectivity would help make analyses more reliable and possibly reduce the costly and time-consuming sample preparation steps that are currently required. Additional development of bioassays to detect CDDs could provide screening methods with sufficient sensitivity to detect the very low concentrations of toxicological importance.

6.3.2 Ongoing Studies

A collaborative study was identified in which researchers at CDC, NIEHS, University of Mainz in Germany and the German Cancer research Center in Heidelberg are studying biochemical markers of exposure and susceptibility to dioxin in human peripheral blood lymphocytes (Yang et al. 1997).

The following information was obtained from a search of Federal Research in Progress (FEDRIP 1998).

Under an SBIR (Small Business Innovative Research) grant, Xeonobiotic Detection Systems, Inc. of Durham, NC, is marketing the CALUX assay (Anonymous 1997) described in Section 6.1. Hybrizyme

Corp, of Raleigh, NC, is working on a new test method for dioxins in human and animal samples. This work is also being performed under an SBIR. No other details were available. Antibody-based methods for 2,3,7,8-TCDD analysis is the subject of a project lead by R. Carlson of Ecochem Research, Inc. (another SBIR) during which methods for gases will be developed. Finally, G. Wheelock, Paracelsian, Inc., Ithaca, NY, is using SBIR funding to develop an Ah receptor-based assay for the determination of toxic equivalency factors.

7. REGULATIONS AND ADVISORIES

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

It is ATSDR's policy (see Appendix B) to use health guidance values (i.e., MRLs and EMEGs) derived for 2,3,7,8-TCDD for other dioxin-like compounds expressed as total TEQs.

ATSDR has derived an acute-duration oral MRL of 0.0002 µg/day (2×10^{-4} µg/kg/day) for 2,3,7,8-TCDD based on its ability to suppress serum total hemolytic complement activity in $B6C3F_1$ mice (White et al. 1986).

An intermediate-duration oral MRL of 0.00002 µg/day (2×10^{-5} µg/kg/day) was derived based on observed decreases in thymus weight in guinea pigs (Decaprio et al. 1986).

A chronic-duration oral MRL of 0.000001 µg/day (1×10^{-6} µg/kg/day) was derived for 2,3,7,8-TCDD based on altered social interactions with peers in monkeys exposed to 2,3,7,8-TCDD prenatally and during lactation (Schantz et al. 1992).

Neither a reference concentration (RfC) nor a reference dose (RfD) is listed in IRIS (IRIS 1998) for any of the CDDs.

The IRIS database does not contain a weight-of evidence cancer classification for 2,3,7,8-TCDD. The EPA is currently in the final stages of re-evaluating the risks and hazards from exposures to CDDs and CDD-like-like compounds. In its proposed rule to add a chemical category that includes dioxin and dioxin-like compounds to the list of toxic chemicals subject to release reporting requirements, EPA acknowledged that existing data shows "2,3,7,8-TCDD is a potent toxicant in animals and has the potential to a produce a wide spectrum of toxic effects in humans" (EPA 1997c). In the preamble of the rule EPA further states that "Available human data cannot clearly demonstrate whether a cause and effect relationship exists between 2,3,7,8-TCDD exposure and increased incidence of cancer. However, there are a number of epidemiological studies associating exposure to 2,3,7,8,-TCDD with cancer mortality" (EPA 1997c). Making reference to the 1985 cancer slope factor (1.56×10^5 $[mg/kg/day]^{-1}$) (EPA 1985d) for

2,3,7,8-TCDD and considering its own weight-of-evidence classification criteria, EPA states that “there is sufficient evidence to conclude that the compound is a probable human carcinogen” (EPA 1997c). In February, 1997, the International Agency for Research on Cancer (IARC) evaluated the evidence for CDDs being risk factors for human cancer (IARC 1997). Consequently, IARC currently identifies 2,3,7,8-TCDD as being carcinogenic to humans; Group 1 carcinogen (IARC 1997). IARC concluded that there is limited evidence in humans for the carcinogenicity of 2,3,7,8-TCDD; however, data from studies involving experimental animals provided sufficient evidence of carcinogenicity. Giving consideration to supporting evidence such as 2,3,7,8-TCDD being a multi-site carcinogen in experimental animals; its acting through a mechanism involving Ah receptor which functions the same way in humans as in experimental animals; and similar tissue concentrations both in heavily exposed human populations and rats exposed to carcinogenic dosages, IARC’s overall evaluation for 2,3,7,8-TCDD is that it is carcinogenic to humans (IARC 1997). The Department of Health and Human Services (DHHS), National Toxicology Program (NTP) considers it to be a substance that is “reasonably anticipated to be a carcinogen.” Again, the supporting data indicate that the evidence of 2,3,7,8-TCDD carcinogenicity in humans is limited, but that there is sufficient evidence of carcinogenic effects in studies involving experimental animals (NTP 1998). NTP is currently considering a reclassification of 2,3,7,8-TCDD and the decision is pending.

EPA regulates dioxins as hazardous air pollutants (HAPs) in accordance with the provisions of the Clean Air Act (CAA). EPA has promulgated guidelines and performance standards limiting dioxin and other HAP emissions from various sources (i.e., major, stationary, and area). A wide variety of health effects (e.g., cancer, respiratory problems, developmental and/or reproductive effects) have been associated with exposure to HAP emissions (EPA 1998c). Some of the sources for which EPA has most recently promulgated or proposed guidelines and standards under the authority of the CAA are municipal waste combustors (MWCs), hospital/medical/infectious/waste combustors (HMIWI), and process operations in the Portland Cement industry (EPA 1997a, 1997b, 1998c).

Owners and operators of facilities that have chemicals subject to "The Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986" on their sites in amounts exceeding a designated “reporting threshold level” are required to annually report releases of such chemicals to any environmental media (U.S. Congress 1986). On May 7, 1997, EPA proposed adding a chemical category that includes dioxin and 27 dioxin-like compounds to the list of toxic chemicals subject to the EPCRA reporting requirements (EPA 1997c).

2,3,7,8-TCDD is also regulated as a drinking water contaminant. As an impurity in the production of some pesticides, 2,3,7,8-TCDD may get into drinking water by industrial discharge of waste. EPA has set a drinking water standard (Maximum Contaminant Level [MCL]) for dioxin at 3×10^{-8} ppm (EPA 1994d). People who drink water containing dioxin in excess of the MCL over many years could experience problems with their reproductive systems and may have an increased risk of cancer (EPA 1998d). There is little to no risk associated with drinking-water that meets the MCL (EPA 1994d). In February 1998, as mandated by the Safe Drinking Water Act (SDWA), EPA issued a proposed rule that would require community water systems to inform the public as to the quality of the water delivered by the system (EPA 1998). The community right-to-know provisions of the SDWA mandate a reporting which informs the public of where their water comes from, shows them the process by which safe drinking water is delivered to their homes, provide access to information concerning source water assessments, and allows them to make informed decisions about their drinking water (EPA 1998d). The SDWA provisions also include requirements for timely notifications of violations. Within 24 hours, people served by public water systems must be notified of any violations of the national drinking water standard that have the potential to have serious adverse health effects (EPA 1998d). The SDWA amendments of 1996 required the FDA to issue monitoring requirements for nine allowable contaminants in bottled water (FDA 1998a, 1998b). 2,3,7,8-TCDD is included among these nine chemicals.

2,3,7,8-TCDD is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: electroplating (EPA 1981a), steam electric power generating (EPA 1982a), and metal finishing (EPA 1986g). Limitations depend on the type of industry and plant. If waters and their sediments become contaminated from sources such as atmospheric deposition and discharges from industrial, municipal, or agricultural operations, toxic substances could concentrate in the tissue of fish and wildlife. Sixty-six advisories have been issued by 21 states recommending consumers limit their consumption of fish and shellfish (EPA 1998b). For 14 states (Wisconsin, Rhode Island, New Hampshire, West Virginia, Louisiana, Arkansas, Virginia, Michigan, Mississippi, Florida, Massachusetts, Oregon, Tennessee, and Delaware) advisories were issued for freshwater fish (EPA 1998b). Only two states (Texas and California) issued advisories for marine waters only (EPA 1998b). An advisory for woodduck (migratory fowl) was issued for the state of Arkansas. This information is current as of December 1997, based on the EPA Fish and Wildlife Advisory Database searched October 1998 at: http://www.epa.gov/OST/fishadvice/. More detailed information can be obtained from the state Public Health Department or the state Department of Natural Resources. A fish or wildlife advisory will specify the bodies of water or hunting areas with restrictions. The advisory will indicate what species and size of fish or game are of concern. The advisory

may completely ban consumption or recommend limiting meals of a certain fish or wildlife species to a particular frequency. For example, an advisory may recommend that a person eat a certain type of fish no more than once a month. The advisory may indicate that only certain parts of the fish or game should be consumed and recommend preparation methods that minimize exposure. Fish and wildlife advisories may also provide restrictions specifically targeting pregnant women, nursing mothers, and young children. Each state, Native American Tribe, or U.S. Territory chooses its own criteria for issuing fish and wildlife advisories.

2,3,7,8-TCDD is regulated as a hazardous waste constituent under the requirements of the Resource Conservation and Recovery Act (RCRA) (EPA 1988d). Non-specific sources of 2,3,7,8-TCDD-containing waste are wastes from the production or manufacturing use of tri-, tetra-, or pentachlorophenols and their pesticide derivatives, discarded or unused formulations containing these compounds, and residues from incineration or thermal treatment of soil contaminated with these compounds. RCRA prohibits land disposal of hazardous waste unless it meets treatment standards established by the EPA. On May 12, 1997, the EPA promulgated universal treatment standards (UTSs) for hazardous constituents in wood preserving waste. These wastes have been assigned EPA hazardous waste codes F032, F034, and F035 (EPA 1997d). The final rule also promulgated a compliance alternative for dioxin constituents in nonwastewater and wastewater forms of F032 waste which allowed combustion to be used as a method of treatment (EPA 1997d).

The Toxic Substance Control Act (TSCA) authorizes the EPA to determine whether the use of a chemical substance is a “significant new use” (EPA 1998e). Once it has been determined that a use of a chemical is a significant new use, it must be reported to the EPA prior to manufacturing, importing, or processing for the new use. The required notice will provide the EPA with an opportunity to evaluate the intended use, and if necessary, to prohibit or limit the activity before it occurs (EPA 1998e). For example, brominated phthalate ester was included among the 163 chemical substances for which the EPA promulgated significant new use rules (SNURs). The toxicity concern for the new use was that when similar chemicals have been incinerated under combustion conditions of municipal incinerators, dibenzodioxins and dibenzofurans were formed (EPA 1998e). Persons providing notice of this new use would need to characterize, through an incineration simulation, the potential for dioxin and furan formation and agree not to exceed the production volume limit without performing the characterization (EPA 1998e).

Table 7-1. Regulations and Guidelines Applicable to CDDs

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification (2,3,7,8-TCDD)	Group 1[a]	IARC 1997
WHO	Total daily intake (TDI) range 2,3,7,8-TCDD or total TEQs	1-4 pg /kg body weight	WHO 1998a WHO 1998b
HCN	Health-based exposure limit (2,3,7,8-TCDD or total TEQs)	1 pg/kg/day	HCN 1996
NATIONAL			
a. Air:			
OSHA	Meets criteria for OSHA medical records (2,3,7,8-TCDD)	Yes	29 CFR 1910.20 OSHA 1987
EPA OAR	Section 112(b) Hazardous Air Pollutant	Yes	Clean Air Act Amendments U.S. Congress 1990
	Standards of Performance for New Stationary Sources Emission guidelines an compliance times for municipal waste combustors	Yes	40 CFR 60, Subpart Cb EPA 1995b
	Emissions Guideline for existing sources and standards of performance for new stationary sources: Large municipal waste combustion units; Final rule	Yes	62 FR 45124 EPA 1997f
	Municipal waste combustors constructed between December 20, 1989 and September 20, 1994	Yes	40 CFR 60, Subpart Ea EPA 1995f
	Municipal waste combustors constructed after September 20, 1994	Yes	40 CFR 60, Subpart Eb EPA 1995d
	Large municipal waste combustion units; emission guidelines; Final rule	Yes	62 FR 45116 EPA 1997a
	National Emission Standards for Hazardous Air Pollutants for Source Categories Wood Furniture Operations	Yes	40 CFR 63, Subpart JJ EPA 1995e
	Hazardous Waste Combustors; Revised Standards—Final rule	Yes	63 FR 33782 EPA 1998i
b. Water:			
EPA OW	Regulated under SDWA of 1986 (2,3,7,8-TCDD)	Yes	FSTRAC 1990
	Guidelines Establishing Test Procedures for the Analysis of Pollutants; EPA Method 1613	Yes	62 FR 48394 EPA 1997g
	Maximum Contaminant Level—2,3,7,8-TCDD (Dioxin)	3.0×10^{-8} mg/L	40 CFR 141 EPA 1994d
	EPA drinking water standard		
	Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals—Best available technologies	Treatment technology required is granular activated carbon	40 CFR 142.62 EPA 1994e

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Permit required for underground injection of 2,3,7,8-TCDD containing wastes designated hazardous under RCRA	Yes	40 CFR 144.1 EPA 1983a
	Hazardous Waste Injection Restrictions Waste specific prohibitions; dioxin-containing wastes	Yes	40 CFR 148.11 EPA 1988h
	Hazardous Waste Injection Restrictions: Treatment Standards for Hazardous Wastes (proposed) (TCDD, PCDD, HCDD)	<1 ppb	40 CFR 148 EPA 1993b
	General pretreatment regulations for existing and new sources of pollution (2,3,7,8-TCDD)	Yes	40 CFR 403.2, App. B EPA 1986d
	Application for an National Pollutant Discharge Elimination System permit (TCDD)	Yes	40 CFR 122.21 EPA 1983b
	Designated as a toxic pollutant under Section 307(a)(1) of the Federal Water Pollution Control Act and is subject to effluent limitations (2,3,7,8-TCDD)	Yes	40 CFR 401.15 EPA 1979c
	Electroplating Point Source Category General definition	Yes	40 CFR 413.02 EPA 1981a
	Steam Electric Power Generating Point Source Category Pretreatment standards for new sources (PSNS)	Yes	40 CFR 423.17 EPA 1982a
	Effluent Limitations Guidelines,Pretreatment Standards, and New Source Performance Standards for the Transportation Equipment Cleaning Point source Category—Proposed rule	Yes	63 FR 34686 EPA 1998f
	Effluent Limitations Guidelines, Pretreatment Standards, and new source performance Standards for the Industrial Waste Combustor Subcategory of the Waste Combustors Point source Category—Proposed rule	Yes	63 FR 6392 EPA 1998g
	Effluent Limitations Guidelines, Pretreatment Standards, and New Source Performance Standards for the Landfill Point source Category— Proposed rule	Yes	63 FR 6426 EPA 1998h
	2,3,7,8-TCDD Excluded from Subcategory 1 - Organic Pesticide Chemicals Manufacturing Regulations	Yes	40 CFR 455 EPA 1978

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
c. Food:			
EPA	Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities concentration limit of 2,3,7,8-TCDD in technical grade hexachlorophene	0.1 ppm	40 CFR 180.302 EPA 1971b
FDA	Requirements for Specific Standardized Beverages Bottled water	3×10^{-8} mg/L	21 CFR 165.110 FDA 1995
	Analysis to determine compliance—Methods for Chemical Analysis of Water and Waste	Method 1613	
d. Other:			
DOT	Designated as a hazardous material subject to requirements for packaging, labeling, and transportation (dioxins)	Yes	49 CFR 172.101, App. A DOT 1989b
EPA OERR	Regulated under the MPRSA; ocean dumping prohibited except when in trace amounts (2,3,7,8-TCDD)	Yes	40 CFR 227.6 EPA 1977
	Reportable quantity (2,3,7,8-TCDD)	1 pound	40 CFR 302.4 EPA 1985g
	Addition of Dioxin and Dioxin-like Compounds; Toxic Chemical Release Reporting; Community Right-to-Know—Proposed rule	Yes	62 FR 24887 EPA 1997c
EPA OPTS	TSCA regulates the use, disposal, and distribution in commerce of process waste water treatment sludges intended for land application from pulp and paper mills employing chlorine or chlorine derivative based bleaching processes (2,3,7,8-TCDD)	Yes	40 CFR 744 EPA 1991f
EPA OSW	Identification and Listing of Hazardous Wastes: (*F033*) Hazardous Wastes from Non-specific Sources (proposed) (TCDD, PCDD, HxCDD, HpCDD, OcCDD)	Yes	58 FR 25706 40 CFR 261.31 EPA 1993c
	Listing as a hazardous constituent (2,3,7,8-TCDD)	Yes	40 CFR 261, App. VIII EPA 1988d
	Hazardous Waste Combustors; Revised Standards—Final rule	Yes	63 FR 33782 (40 CFR 262 and 270) EPA 1998i
	Identification and Listing of Hazardous Wastes: Wastes Excluded Under 260.20 and 260.22 (TCDD, PCDD, HxCDD, HpCDD)	Yes	40 CFR 261, App. IX EPA 1984d

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities Performance standards for incinerators	Yes	40 CFR 264.343 EPA 1981b
	Groundwater monitoring requirement (dioxins)	Yes	40 CFR 264, App. IX EPA 1987b
	Recyclable Materials Used in a Manner Constituting Disposal Standards applicable to users	Yes	40 CFR 266.23 EPA 1985h
	Interim status standards for burners	Yes	40 CFR 266.103 EPA 1991g
	Standards to control organic emissions, hazardous waste codes F021, F022, F023, F026, and F027	99.9999% DRE	40 CFR 266.104 EPA 1991h
	Hazardous Waste Burned in Boilers and Industrial Furnaces Regulation of residues	Yes	40 CFR 266.112 EPA 1985i
	Procedure for Estimating the Toxicity Equivalency of Chlorinated dibenzo-p-dioxin and dibenzofuran congeners	Yes	40 CFR 266, App. IX EPA 1989f
	Land disposal of certain dioxin-containing wastes prohibited (2,3,7,8-TCDD)	Yes	40 CFR 268.31 EPA 1988f
	Land Disposal Restrictions Treatment Standards for hazardous waste—waste code F032	Wastewaters 6.3×10^{-5} mg/L or combustion Nonwastewaters 0.001 mg/L or combustion	62 FR 25998 EPA 1997d
	Land Disposal Restrictions	Yes	40 CFR 268.48 EPA 1991i
	Prohibitions on storage of restricted wastes	Yes	40 CFR 268.50 EPA 1986l
	Land Disposal Restrictions: List of Halogenated Organic Compounds Regulated Under 268.32 (PCDD, TCDD, HxCDD)	Yes	40 CFR 268, App. III EPA 1987m
Guidelines:			
a. Air:			
NIOSH	C_a = Potential Human Carcinogen	Carcinogen; lowest feasible concentrations	NIOSH 1997
b. Water:			
EPA ODW			
	MCLG in drinking water (2,3,7,8-TCDD)	Zero	EPA 1995a

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Health Advisories (2,3,7,8-TCDD):		EPA 1996a
	1-day (child)	$1.0x10^{-6}$ mg/L ($1.0x10^{-3}$ µg/L)	
	10-day (child)	$1.0x10^{-7}$ mg/L ($1.0x10^{-4}$ µg/L)	
	Longer term (child)	$1.0x10^{-8}$ mg/L ($1.0x10^{-5}$ µg/L)	
	Longer term (adult)	$4.0x10^{-8}$ mg/L ($4.0x10^{-5}$ µg/L)	
	10^{-4} Cancer risk level	$2.0x10^{-8}$ mg/L ($2.0x10^{-5}$ µg/L)	
EPA OW	Ambient Water Quality Criteria for Protection of Human Health:		EPA 1984a
	Ingesting water and organisms (2,3,7,8-TCDD):		
	10^{-5}	$1.3x10^{-7}$µg/L	
	10^{-6}	$1.3x10^{-8}$ µg/L	
	10^{-7}	$1.3x10^{-9}$ µg/L	
	Ingesting organisms only (2,3,7,8-TCDD):		
	10^{-5}	$1.4x10^{-7}$ µg/L	
	10^{-6}	$1.4x10^{-8}$ µg/L	
	10^{-7}	$1.4x10^{-9}$ µg/L	
NAS	ADI (2,3,7,8-TCDD)	10^{-4} µg/kg/day	NAS 1977
c. Food:			
FDA	Levels in fish (2,3,7,8-TCDD):		EPA 1985d
	No serious health effects	<25 ppt	
	Fish should not be consumed	>50 ppt	
d. Other:			
EPA	RfD (oral)	Not Determined	IRIS 1998
	Carcinogen classification (HxCDD)	B2[c]	EPA 1996a
	Unit risk (air) (HxCDD)	1.3 µg/m^3	IRIS 1998
	Unit risk (water) (HxCDD)	$1.8x10^{-1}$ (µg/L)$^{-1}$	
NTP	Cancer Classification—Reasonably anticipated to be a human carcinogen	Limited evidence in humans; sufficient evidence in animals	NTP 1998
FDA	Risk-specific dose	0.057 pg/kg/day	FDA 1990
DHHS	Risk-specific dose for total TEQs	0.057 pg/kg/day	PHS 1992
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable Ambient Air Concentrations		NATICH 1992
AZ	(1 hour) (2,3,7,8-TCDD)	$4.2x10^{-2}$µg/m^3	
	(24 hour) (2,3,7,8-TCDD)	$1.1x10^{-2}$µg/m^3	
	(Annual) (2,3,7,8-TCDD)	$3.0x10^{-5}$µg/m^3	
FL - Pinella	(Annual) (2,3,7,8-TCDD)	$2.2x10^{-8}$µg/m^3	
IN	(Annual) (2,3,7,8-TCDD)	$3.0x10^{-8}$ µg/m^3	
KS	(1 year) (2,3,7,8-TCDD)	$3.03x10^{-8}$µg/m^3	
ME	(24 hour) (2,3,7,8-TCDD)	$3.5x10^{-6}$µg/m^3	
	(Annual) (2,3,7,8-TCDD)	$2.5x10^{-7}$µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
STATE (cont.)			
MI	(Annual) (2,3,7,8-TCDD)	$2.3x10^{-8}$ µg/m^3	
NC	(Annual) (2,3,7,8-TCDD)	$3.01x10^{-6}$ µg/m^3	
NC - Forco	(Annual) (2,3,7,8-TCDD)	$8.00x10^{-6}$ µg/m^3	
ND	(2,3,7,8-TCDD) (avg. time NA)	$4.5x10^{-1}$ µg/m^3	
PA - Phil	(1 year) (2,3,7,8-TCDD) (Annual) (2,3,7,8-TCDD)	$1.00x10^{-4}$ µg/m^3 $3.50x10^{-5}$ µg/m^3	
VA	(24 hour) (2,3,7,8-TCDD)	3.00 µg/m^3	
VT	(Annual) (dioxins)	$2.00x10^{-2}$ µg/m^3	
KY	Significant emission levels of toxic air pollutants (2,3,7,8-TCDD)	$5.1x10^{-7}$ pounds/hour	401 KAR 63:022 NREPC 1986
WA - SW	(Annual) (2,3,7,8-TCDD)	$3.0x10^{-6}$ µg/m^3	NATICH 1992
WI	Hazardous air contaminants without acceptable ambient concentrations (2,3,7,8-TCDD)	.0001 pounds/year	WAC 1988
b. Water:			
CA	Water Quality Standards; Establishment of Numeric Criteria for Priority Toxic Pollutants for the State of California—Porposed rulex	Yes	62 FR 42160 EPA 1997
FL	Drinking water monitoring for unregulated contaminants (2,3,7,8-TCDD)	Yes	CELDS 1994
KS	Applied action levels for groundwater (2,3,7,8-TCDD)	2 pg/L	KBWP 1988
	Drinking Water Quality Guidelines and Standards (2,3,7,8-TCDD)	$2.2x10^{-6}$ µg/L	FSTRAC 1990
ME	Drinking Water Quality Guidelines and Standards (2,3,7,8-TCDD)	$2.2x10^{-6}$ µg/L	FSTRAC 1990
MO	Surface water criterion (2,3,7,8-TCDD): Aquatic life Drinking water supplies	 0.014 pg/L 0.130 pg/L	10 CSR 20-7.031 MDNR 1987
MN	Recommended allowable limits (proposed) (2,3,7,8-2,3,7,8-TCDD)	20 pg/L	MWQS 1988a
	Chronic criteria (proposed) (2,3,7,8-TCDD): Groundwater Surface water	 2 pg/L 0.002 pg/L	MWQS 1988b
NH	Drinking Water Guideline	$2x10^{-7}$ µg/L	FSTRAC 1990
NY	Ambient water quality standard aquatic life (2,3,7,8-TCDD) Maximum concentration level in drinking water (2,3,7,8-TCDD) Water quality standard (2,3,7,8-TCDD)	1 pg/L 5 µg/L 1 pg/L	NYWQSGV 1987; NYPDWS 1989
RI	Drinking Water Guideline	$2x10^{-7}$ µg/L	FSTRAC 1990
SD	Maximum allowable concentrations in ground water (2,3,7,8-TCDD)	0	SDGWQS 1989

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
STATE (cont.)			
VT	Groundwater protection regulations (2,3,7,8-TCDD):		VANR 1988
	Preventive action limit	$2x2^{-8}$ µg/L	
	Enforcement standard	$2x2^{-7}$ µg/L	
WI	Human cancer criteria (2,3,7,8-TCDD):		WDNR 1987
	Public water supply:		
	Warm water sport fish communities	0.097 pg/L	
	Cold water communities	0.03 pg/L	
	Great Lakes communities	0.03 pg/L	
		0.1 pg/L	
		450 pg/L	
	Non-water supply:		
	Warm water sport communities		
	Cold water communities		
	Warm water forage and limited forage fish communities and limited aquatic life		
	Water Quality Criteria: Human Health		
AZ	Domestic Water Source	$2x10^{-7}$ µg/L	CELDS 1994
	Fish Consumption	$4x10^{-9}$ µg/L	
	Fullbody contact	$9x10^{-6}$ µg/L	
CT	Consumption of Organisms	$1.4x10^{-9}$ µg/L	
	Consumption of Water and Organisms	$1.3x10^{-9}$ µg/L	
	Health Designation	C-HB[d]	
DE	Freshwater Fish Ingestion	$1.7x10^{-6}$ ng/L	
	Freshwater Fish and Water Ingestion	$1.6x10^{-6}$ ng/L	
	Marine/Estuarine Fish/Shellfish Ingestion	$2.4x10^{-7}$ ng/L	
	Human Health Concern (carcinogen)	CA	
IN	Continuous Criterion Concentration (4-d avg.)		
	Outside mixing zone	$1x10^{-7}$ µg/L	
	Point of water intake	$1x10^{-7}$ µg/L	
KY	Fish Consumption	$1.4x10^{-9}$ µg/L	
	Domestic Water Supply	$1.3x10^{-9}$ µg/L	
MO	Fish Consumption	$1.4x10^{-6}$ ng/L	
	Drinking Water Supply	$1.3x10^{-6}$ ng/L	
	Groundwater	$1.3x10^{-6}$ ng/L	
NY	Groundwater	$3.5x10^{-6}$ µg/L	
OH	Outside Mixing Zone (30-d avg.)	0.14 pg/L	
OR	Water and Fish Ingestion	$1.3x10^{-6}$ ng/L	
	Fish Ingestion	$1.4x10^{-6}$ ng/L	
SD	Domestic Water Supply	$1.3x10^{-9}$ µg/L	
	All Others	$1.4x10^{-9}$ µg/L	

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
STATE (cont.)			
VT	Class A or B Waters	1.3×10^{-6} ng/L	
	Class C Waters	1.4×10^{-6} ng/L	
WI	Public Water Supplies		
	Warm Water	0.097 pg/L	
	Cold Water	0.03 pg/L	
	Great Lakes	0.03 pg/L	
	Non-public Water Supplies		
	Warm Water Sport	0.1 pg/L	
	Cold Water Forage	0.3 pg/L	
	Groundwater	450 pg/L	
	Groundwater	2.2×10^{-8} µg/L	
	Water Quality Criteria: Aquatic Life		
AZ	Acute-Cold Water Fishery	0.01 µg/L	CELDS 1994
	Acute-Warm Water Fishery	0.01 µg/L	
	Acute-Effluent Dominated Water	0.12 µg/L	
	Acute-Ephemeral	0.1 µg/L	
	Chronic-Coldwater Fishery	0.005 µg/L	
	Chronic-Warm Water Fishery	0.005 µg/L	
	Chronic-Effluent Dominated Water	0.01 µg/L	
	Chronic-Ephemeral	0.01 µg/L	
HI	Acute-Freshwater	0.03 µg/L	
	Fish Consumption	5×10^{-9} µg/L	
OR	Acute-Freshwater	0.01 µg/L	
	Chronic-Freshwater	38 pg/L	
	Water Quality Criteria: Recreational Use		
TN		1×10^{-6} ng/L	
	Groundwater Monitoring		
IL		Yes	CELDS 1994
LA		Yes	
MN		Yes	
WV		Yes	
WI		Yes	

	Fish and Wildlife Advisories	Number of Advisories Issued for 1997		
		Fish	Wildlife	
AR	Freshwater	1	1 (wood duck)	EPA 1998b
CA	Saltwater	1		
DE	Freshwater	1		
FL	Freshwater	1		
LA	Freshwater	2		
MA	Freshwater	1		

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
STATE (cont.)			
ME	Freshwater and saltwater (statewide)	8	EPA 1998a EPA 1998b
MI	Freshwater	8	EPA 1998b
MS	Freshwater	1	
NC	Freshwater and Saltwater	5	
NH	Freshwater	1	
NJ	Freshwater and Saltwater (statewide)	9	EPA 1998a EPA 1998b
NY	Freshwater and Saltwater (statewide)	10	EPA 1998a EPA 1998b
OR	Freshwater	1	EPA 1998b
RI	Freshwater	1	
TN	Freshwater	1	
TX	Saltwater	1	
VA	Freshwater	2	
WA	Freshwater and Saltwater	2	
WI	Freshwater	2	
WV	Freshwater	6	
c. Food:			
WI	Health standards for contaminants commonly found in sport fish (2,3,7,8-TCDD)	50 ppt	WAC 1988
d. Other:			
	Hazardous Constituent		
CA	Total Threshold Limit Concentration Toxic Materials Limits (30-d avg.)	1 mg/kg 0.0039 pg/L	CELDS 1994
CO		Yes	
IL		Yes	
KY	Defined as hazardous waste constituent (dioxins)	Yes	401 KAR 31:160 NREPC 1988
	Dioxin-containing wastes are prohibited from land disposal (dioxins)	Yes	401 KAR 37:030 NREPC 1988
	Treatment standards; constituent concentration in waste extract (dioxins)	<1 ppb	401 KAR 37:040 NREPC 1988
LA		Yes	CELDS 1994
MA		Yes	
MN		Yes	
ND		Yes	
WV		Yes	

Table 7-1. Regulations and Guidelines Applicable to CDDs (continued)

Agency	Description	Information	References
STATE (cont.)			
WI		Yes	
	Groundwater Effluent Standards		
NY		$3.5x10^{-6}$ µg/L	CELDS 1994

[a] Group 1: carcinogenic to humans
[b] Because of its carcinogenic potential the EPA-recommended concentration for dioxins in ambient water is zero. However, because attainment of this level may not be possible, levels that correspond to upper-bound incremental lifetime cancer risks of 10^{-5}, 10^{-6}, and 10^{-7} are estimated.
[c] Group B2: probable human carcinogens
[d] C: Carcinogenic (probable or possible); HB: high potential to bioaccumulate or bioconcentrate

ADI = Acceptable Daily Intake; CELDS = Computer-environment legislative data systems database. CDDs = chlorinated dibenzo-p-dioxins; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FR = Federal Register; HCN = Health Council of the Netherlands; HxCDD = Hexachlorodibenzo-p-dioxin; IARC = International Agency for Research on Cancer; KBWP = Kansas Bureau of Water Protection; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; MDNT = Missouri Department of Natural Resources; MPRSA = Marine Protection Research and Sanctuaries Act; MWQS = Minnesota Water Quality Standards; NAS = National Academy of Sciences; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; NREPC = National Resources and Environmental Protection Cabinet; NYPDWS = New York Public Drinking Water Standards; NYWQSGV = New York Water Ambient Quality Ambient Standards and Guidance Values; OAR = Office of Air and Radiation; OCDD = octachlorodibenzo-p-dioxin; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Programs; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OPTS = Office of Pesticides and Toxic Substances; OW = Office of Water; Penta-CDD = Pentachlorodibenzo-p-dioxin; RCRA = Resource Conservation and Recovery Act; RfD = Reference Dose; SDGWQS = South Dakota Ground-Water Quality Standards; SDWA = Safe Drinking Water Act; TEQ = TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin; TDI = Tolerable Daily Intake; TSCA = Toxic Substance Control Act; VANR = Vermont Agency of Natural Resources; WAC = Wisconsin Administrative Code; WDNR = Wisconsin Department of Natural Resources; WHO = World Health Organization

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9. GLOSSARY

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

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—are functional changes in the immune response.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pharmacokinetics—is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information 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) concentrations for up to a 10-hour workday during a 40-hour workweek.

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

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

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

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 a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MRL WORKSHEET

Chemical Name: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Number: 1746-01-6
Date: December 10, 1998
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [] Chronic
Key to Figure: 78m
Species: Mice

Minimal Risk Level: 0.0002 (2×10^{-4}) [X] µg/kg/day [ ] ppm

Reference: Burleson et al. 1996

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 20 female B6C3F1 mice were administered a single gavage dose of 0, 0.001, 0.005, 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD in corn oil. Seven days after 2,3,7,8-TCDD exposure, the mice were infected intranasally with influenza A/Hong Kong/8/68 (H3N2) virus diluted at 10^{-48}, 10^{-50}, 10^{-52}, or 10^{-54}. In a separate experiment, groups of 18 female mice received a single gavage dose of 0, 0.001, 0.01, or 0.1 µg/kg 2,3,7,8-TCDD and were infected 7 days later with influenza A virus at a dose not known to cause mortality (10^{-54} and 10^{-58}) or were sham-infected. Body weight, thymus weight, and wet lung weights were measured 3, 9, or 12 days postinfection. Pulmonary virus titers were determined in groups of 72 mice exposed to 0, 0.001, 0.01, or 0.01 µg/kg 2,3,7,8-TCDD and infected with influenza A virus seven days later. For the virus titer study, groups mice were killed 2 hours, 1, 4, 6, 7, 8, 9, 10, and 11 days post-infection.

Effects noted in study and corresponding doses:

Statistically significant increases in mortality were observed in the influenza A infected mice exposed to 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD. However, no between group differences in mortality were observed at these 2,3,7,8-TCDD dosages. Mortality in mice receiving 0.001 or 0.005 µg/kg did not significantly differ from the mortality in the control group. Exposure to 2,3,7,8-TCDD did not enhance the increase in relative lung weight normally seen in mice infected with influenza A virus. As compared to controls, no significant alterations in thymus weights were observed in 2,3,7,8-TCDD-exposed mice sham-infected or those infected with influenza A virus. 2,3,7,8-TCDD exposure did not result in a significant increase in viral titers in the lung, as compared to titers from the control group. The authors noted that the lack of dose-response in mortality and the lack of effect on the relative lung weight, thymus weight, and viral titers suggest that 2,3,7,8-TCDD may be exerting an effect via an indirect mechanism such as through an effect on cytokines.

Dose and end point used for MRL derivation: Impaired resistance to influenza A virus infection, as evidence by the significant increase in mortality, was observed in female $B6C3F_1$ mice administered a single gavage dose of $0.01 µg/kg. No significant effects were observed at lower doses. Thus, 0.005 and 0.01 µg/kg are the NOAEL and LOAEL, respectively, for impaired resistance.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans- A comparison of species sensitivity suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No. A modifying factor of 0.7 was applied to adjust for the difference in higher bioavailability of 2,3,7,8-TCDD from gavage with an oil vehicle than from food. Support for this modifying factor comes from toxicokinetic studies in Sprague Dawley rats. In rats fed 0.35 or 1 µg/kg/day 2,3,7,8-TCDD in the diet for 42 days, approximately 60% of the administered dose was absorbed (Fries and Marrow 1975). In contrast, 70-84% of a single or repeated gavage dose of 0.01-50 µg/kg 2,3,7,8-TCDD in corn oil was absorbed in rats (Piper et al. 1973; Rose et al. 1976). Thus, the ratio of 2,3,7,8-TCDD absorption from the diet to gavage with an oil vehicle is 0.71-0.85.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

2,3,7,8-TCDD is a known immunosuppressant in animals in acute-, intermediate, and chronic-duration studies (Kerkvliet 1995). Suppression of the antibody response to sheep erythrocytes was observed in B6C3F1 mice administered 14 daily doses of 0.1 µg 2,3,7,8-TCDD/kg/day (Holsapple et al. 1986), and a significant increase in mortality was observed in $B6C3F_1$ mice administered 1.0 µg/kg/day 2,3,7,8-TCDD for 14 days and challenged with *Streptococcus pneumoniae* (White et al. 1986). Decreased survival after viral infection was also reported in female B6C3F1 mice after a single intraperitoneal dose of 0.1 µg 2,3,7,8-TCDD/kg (House et al. 1990). A significant suppression of complement hemolytic activity was observed in mice administered 0.01 µg/kg/day via gavage for 14 days (White et al. 1986). Furthermore, 2,3,7,8-TCDD alters the immune system of offspring when exposed through lactation and/or *in utero*. For example, a dose-related decrease in relative thymus weights were seen in offspring of rats dosed at levels of 0.005-0.35 µg 2,3,7,8-TCDD/kg on day 16 of pregnancy (Madsen and Larsen 1979).

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MRL WORKSHEET

Chemical Name: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Number: 1746-01-6
Date: December 10, 1998
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [] Chronic
Key to Figure: 187g
Species: Guinea pig

Minimal Risk Level: 0.00002 (2×10^{-5}) [X] µg/kg/day [ ] ppm

Reference: DeCaprio et al. 1986

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of weanling Hartley guinea pigs (10/sex) were administered a diet containing 2, 10, 76 or 430 ppt for 90 days. These diets provided an average of 0.0001, 0.0007, 0.005, or 0.028 µg 2,3,7,8-TCDD/kg/day. The average doses were estimated by the investigators. A group of control guinea pigs was fed a diet without added 2,3,7,8-TCDD. Body weights and food consumption were monitored throughout the experiment. At the end of the dosing period the animals were sacrificed and clinical chemistries, hematology, organ weights and histopathology examinations were performed. The recovery following treatment was studied in groups of 10 guinea pigs fed a diet containing 430 ppt 2,3,7,8-TCDD for 11, 21, or 35 days and allowed to recover for 79, 69, or 55 additional days, respectively.

Effects noted in study and corresponding doses:

The highest dietary level of 2,3,7,8-TCDD caused net body weight loss and mortality. Four males and four females died and additional animals had to be sacrificed due to poor health. Food consumption was significantly reduced in the highest dose group only. Body weight gain in the 0.0007 and 0.005 µg/kg/day male groups was reduced by 9% and 20%, respectively. In the corresponding female groups, body weight gain was reduced by 6% and 15%. Gross lesions were observed only in the highest dose group and included thymic atrophy, depletion of body fat, and liver enlargement. Significant changes in organ weights included a decrease in absolute kidney weight and in absolute and relative thymus weight in males dosed with 0.005 µg/kg/day, increase in relative liver weight in males and females at the 0.005 µg/kg/day level, and increase in relative brain weight in males at this same dose level. Organ weights from high dose animals were not monitored. Administration of 2,3,7,8-TCDD did not cause any significant hematological effect (blood was not collected from the highest dose group). In the 0.005 µg/kg/day groups, serum ALT was significantly reduced in females whereas triglycerides were elevated in males. No other significant changes in clinical chemistries were observed. Treatment-related histological alterations were observed only in the two higher dose groups and consisted of hepatocellular cytoplasmic inclusion bodies and atrophy of the thymic cortex. In the recovery study there was 10% mortality in the groups treated for 11 and 21 days and 70% mortality in the group treated for 35 days. Surviving animals in all groups exhibited significantly reduced body weight gain.

Dose and end point used for MRL derivation: The dose of 0.0007 µg/kg/day represents a NOAEL for decreased thymus weight, whereas the 0.005 µg/kg/day is a LOAEL.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans-A comparison of species sensitivity suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No. The doses were estimated by the investigators.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

2,3,7,8-TCDD is a known immunosuppressant in animals in acute-, intermediate, and chronic-duration studies (Kerkvliet 1995). Reduction of thymus weight was also observed in intermediate-duration oral studies in rats (Van Birgelen et al. 1995; Viluksela et al. 1994). Another sensitive species for immunological effects of 2,3,7,8-TCDD is the marmoset monkey in which alterations in lymphocyte subsets have been reported after subcutaneous application of an average 0.0015 µg 2,3,7,8-TCDD/kg/day for 26 weeks (Neubert et al. 1992). Furthermore, 2,3,7,8-TCDD alters the immune system of offspring when exposed through lactation and/or *in utero*. For example, a dose-related decrease in relative thymus weights were seen in offspring of rats dosed at levels of 0.005-0.35 µg 2,3,7,8-TCDD/kg on day 16 of pregnancy (Madsen and Larsen 1979).

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MRL WORKSHEET

Chemical Name: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Number: 1746-01-6
Date: December 10, 1998
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 226k
Species: Monkey

Minimal Risk Level: 0.000001 (1×10^{-6}) [X] µg/kg/day [ ] ppm

Reference: Schantz et al. 1992

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 8 female rhesus monkeys were fed a diet containing 0, 5, or 25 ppt 2,3,7,8-TCDD for a total of 16.2 ± 0.4 months. After 7 months of exposure, the monkeys were mated with unexposed males. (Only 1 monkey in the 25 ppt group delivered a viable offspring; this offspring was not studied behaviorally). The monkeys were fed the 2,3,7,8-TCDD diet throughout the mating period, gestation, and lactation. The authors estimated that the total 2,3,7,8-TCDD intake over the course of the study was 59.6 ± 5.0 ng/kg for the 5 ppt group. The offspring were weaned at 4 months and individually housed. Mesenteric fat samples were collected from the offspring at age 5 months; the average 2,3,7,8-TCDD levels in the fat samples was 377 ±141 ppt (range of 290-950) for the 5 ppt group and below the detection limit of 2-200 ppt for the controls. When the offspring were 8.6 months of age, they were placed in peer groups of 4 monkeys and allowed to play for 1.5 hours without interference. The peer groups consisted of two 2,3,7,8-TCDD-exposed monkeys and two control monkeys. Behavioral patterns (social interactions and other behaviors such as vocalization, locomotion, self-directed behavior and environmental exploration) were monitored 4 days/week for 9 weeks.

Effects noted in study and corresponding doses:

No overt signs of toxicity were observed in the mothers or offspring, and birth weights and growth were not adversely affected by 2,3,7,8-TCDD exposure. Significant alterations were observed in play behavior, displacement, and self-directed behavior in the 2,3,7,8-TCDD -exposed offspring. 2,3,7,8-TCDD-exposed monkeys tended to initiate more rough-tumble play bouts and retreated less from play bouts than controls, were less often displaced from preferred positions in the playroom than the controls, and engaged in more self-directed behavior than controls. No other significant alterations in behavior were observed.

Dose and end point used for MRL derivation:

Although the mothers were exposed to 5 or 25 ppt 2,3,7,8-TCDD, only the offspring from the 5 ppt group underwent behavioral testing. The 5 ppt dietary concentration is equivalent to a daily dose of 1.2×10^{-4} µg/kg/day. This dose is a LOAEL for altered social behavior.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans A comparison of species sensitivity suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.
[X] 10 for human variability.

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Monkeys were exposed to a dietary concentration of 5 ppt 2,3,7,8-TCDD; the authors estimated that the total maternal intake during the 16.2 months of exposure (492 days) was 59.6 ng/kg.

Daily dose = (59.6 ng/kg) / (492 days) = 0.12 ng/kg/day (1.2×10^{-4} µg/kg/day)

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

A behavioral teratology test battery was performed in monkey infants exposed to 2,3,7,8-TCDD during gestation and lactation; the results of this test battery was published in a series of papers (Bowman et al. 1989a; Schantz and Bowman 1989; Schantz et al. 1992). No significant alterations in reflex development, visual exploration, locomotor activity, or fine motor control were found (Bowman et al. 1989a). In tests of cognitive function, object learning was significantly impaired, but no effect on spatial learning was observed (Schantz and Bowman 1989). When the monkey infants were placed in social groups, altered social behavior was observed (Bowman et al. 1989a; Schantz et al. 1992). Additional data on the neurodevelopmental toxicity of 2,3,7,8-TCDD are limited to a study in which prenatal exposure to 2,3,7,8-TCDD resulted in masculinized behavior in female rats (Schantz et al. 1991). No chronic duration animal neurotoxicity studies were located, decreased motor activity was reported in rats acutely exposed to 2 (Giavini et al. 1983) or 5 (Seefeld et al. 1984a) µg/kg/day. The Schantz and Bowman studies are the only available chronic developmental toxicity studies. Acute and intermediate duration studies provide evidence that 2,3,7,8-TCDD is a potent developmental toxicant. Other sensitive developmental effects that have been observed included cleft palate [lowest LOAEL- 0.1 µg/kg/day (Giavini et al. 1982)], hydronephrosis [lowest LOAEL- 1 µg/kg (Moore et al. 1973)], immunosuppression [lowest LOAEL- 0.005 µg/kg (Madsen and Larsen 1979)], impaired development of the reproductive system [lowest LOAEL- 0.064 µg/kg (Mably et al. 1992a, 1992b, 1992c)], and increased newborn mortality [lowest LOAEL-0.7 µg/kg (Bjerke et al. 1994a)]; NOAELs were not identified for these effects in the most sensitive species or strain.

Some human studies have reported effects on the central and peripheral nervous systems shortly after exposure to high levels of 2,3,7,8-TCDD (Filippini et al. 1981; Moses et al. 1984; Pazderova-Vejlupkova et al. 1981; Pocchiari et al. 1979; Suskind 1977). However, follow-up studies did not find neurological effects years after exposure termination (Barbieri et al. 1988), suggesting that the effects may be transient. No human studies examined the effect of 2,3,7,8-TCDD on the developing neurologic system.

It should be also noted that 10 years after termination of 2,3,7,8-TCDD exposure in the Schantz et al. (1992) study, Rier et al. (1993) reported a dose-related increase in the incidence and severity of endometriosis in these same rhesus monkeys. Rier et al. (1993) identified a less serious LOAEL of 5 ppt (0.00012 μg/kg/day) for moderate endometriosis. However, monkeys appear to be more susceptible to endometriosis, based on a background incidence of endometriosis in monkeys of 30% (Rier et al. 1993) compared to a background incidence of 10% in humans (Wheeler et al. 1992). Thus, derivation of a chronic oral MRL based on endometriosis would necessitate using an uncertainty factor of less than 1 (or at most, 1) to account for the increased sensitivity of monkeys to endometriosis as compared to humans. If the Rier et al. (1993) study was used to calculate an oral MRL, the LOAEL of 0.00012 μg/kg/day would be divided by an uncertainty factor of 100 (10 to extrapolate from a LOAEL, 10 for human variability and 1 for interspecies differences). This would result in a computed MRL essentially the same as the chronic oral MRL of 1 pg/kg/day based on developmental toxicity as described in the preceding paragraph. Moreover, (1) the clinical history for these rhesus monkeys during the 10 year period between the Schantz et al. (1992) study and examination by Rier et al. (1993) is unknown (not reported); (2) Boyd et al. (1995) did not find an association between exposure to CDDs, CDFs, or PCBs and endometriosis in a clinical study in women; and (3) the EPA (1997) concluded that "the evidence for supporting the hypothesis that CDDs and PCBs are causally related to human endometriosis via an endocrine-disruption mechanism is very weak." So, even though there is information to indicate that endometriosis may also be a sensitive toxicological end point for 2,3,7,8-TCDD exposure, the developmental end point (altered social behavior) reported in the Schantz et al. (1992) study was determined to be the most appropriate end point for derivation of an MRL for chronic oral 2,3,7,8-TCDD exposure.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX B

Update to the ATSDR Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil

Purpose

The Agency for Toxic Substances and Disease Registry (ATSDR) is updating its *Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil*.

The objective of this update is to ensure that ATSDR health assessors evaluate dioxin levels that exceed the ATSDR established screening level of 0.05 ppb as described in the ATSDR Public Health Assessment Guidance Manual (PHAGM) (ATSDR 2005). The 0.05 ppb value should be used as the comparison value when following the PHAGM. The comparison value is not a threshold for toxicity and should not be used to predict adverse health effects (ATSDR 2005).

This update replaces Appendix B in the Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs) (December, 1998). It does not reflect a change in ATSDR's scientific assessment on dioxin toxicity or the ATSDR Minimal Risk Level (MRL). This update does not impact the EPA guidance which continues to identify 1 ppb as the preliminary remediation goal for residential exposure scenarios. (EPA 1998).

History of the Dioxin Policy Guideline

In 1998, ATSDR adopted a Policy Guideline for Dioxin and Dioxin-like Compounds (ATSDR, 1998). The policy was developed to guide health assessors in evaluating the public health implications of dioxin and dioxin-like compounds (including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and other structurally related halogenated aromatic hydrocarbons) in residential soils near or on hazardous waste sites. The 1998 guideline established three levels as criteria for comparing dioxin levels in residential soil:

- a **screening level**,
- an **evaluation level**, and
- an **action level**.

The 1998 guideline also recommended specific considerations for public health actions within each of these levels.

Since the release of the Policy Guideline in 1998, ATSDR issued the PHAGM. By issuing this update to the guideline, ATSDR is ensuring that health assessors will use the screening level as the appropriate comparison value for following the PHAGM, rather than the "action level" described in the earlier version of this policy guidance. This does not reflect a change in dioxin science; it is simply a reiteration to ensure that the appropriate value is used as a starting point when following the procedures described in the PHAGM.

If health assessors follow the PHAGM, the evaluation and action levels values, as set in 1998, are no longer necessary.

Changes Being Made to the ATSDR Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil

The specific changes to the policy guideline, the reason for those changes, and the expected impact of those changes are summarized in the following table:

Change	Reason for Change	Impact of Change
Elimination of the "evaluation level" and the "action level"	Confusion about interpretation of the evaluation and action levels was a barrier to a more consistent evaluation of exposure to dioxin in residential soils.	This change brings the guidelines up-to-date with ATSDR's PHAGM which uses only screening levels The public health actions described in the 1998 policy guideline remain options that may be applied as appropriate rather than being triggered by a prescribed soil concentration. The minimal risk level (MRL) for dioxin exposure described in the 1998 Toxicological Profile remains the same.
Ensure consistency with ATSDR PHAGM	PHAGM was not referenced in the previous policy.	Consistency with 2005 PHAGM will ensure more comprehensive evaluation, for instance assessing both direct and indirect exposure pathways should result in a more comprehensive evaluation of exposure conditions at sites with dioxin contamination.

Summary

This policy update replaces Appendix B in the Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs) (December, 1998). ATSDR will no longer refer to an Action Level for dioxin in these evaluations. The 0.05 ppb screening level is retained as an initial comparison value for health assessments. The update does not change the assessment of health hazards associated with dioxin exposure, as summarized in the 1998 ATSDR Toxicological Profile and in the derivation of the Minimal Risk Level (MRL). The policy update impacts site-specific health assessments evaluating exposure to dioxin directly from residential soils. The update ensures consistency in the methodology ATSDR uses for site-specific evaluations of health risks for all chemicals.

EPA's preliminary remediation goal for dioxin in soil has not changed and remains at 1 ppb. ATSDR does not establish clean-up goals or preliminary remediation goals, but ATSDR believes that health risks associated with levels of dioxins in soil below 1 ppb would be low under most scenarios where the primary exposure pathway is incidental ingestion through direct exposure to soil. In such instances, ATSDR public health recommendations may include community health education or limiting access to contaminated areas. Consistency with 2005 PHAGM also ensures that a comprehensive evaluation of dioxins from contaminated soils includes the consideration of scenarios where dioxins may enter the food chain pathway.

References

ATSDR. 1998. Toxicological profile for Chlorinated Dibenzo-p-Dioxins. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR. 2005. Public health assessment guidance manual. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

EPA. 1998. Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites. Washington, DC: US Environmental Protection Agency. OSWER Directive 9200.4-26; April 13, 1998.

APPENDIX C

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 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 No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

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

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

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

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-Tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

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

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific 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 8 of the profile.

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

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

LEGEND

See Figure 2-1

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

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

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

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

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

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

SAMPLE

1 6

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Chapter 2 (Section 2.5)

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive 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 NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX D

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4,5-TCP	2,4,5-trichlorophenol
AAH	arylhydrocarbon hydroxylase
ACGIH	American Conference of Governmental Industrial Hygienists
ACOH	acetanylide-4-hydroxylase
ACTH	adenocorticotropin
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
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
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
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CTL	cytotoxic T-lymphocyte
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare

DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DTH	delayed-type hypersensitivity
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EGF	epidermal growth factor
EPA	Environmental Protection Agency
EROD	ethoxyresorufin-O-deethylase
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
FSH	follicle-stimulating hormone
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GGT	gamma-glutamyl transferase
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HDL	high density lipoprotein
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton

K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LDL	low density lipoprotein
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LH	lteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MFO	mxed-function oxidase
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NK cells	natural killer cells
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey

NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEPCK	phosphoenolpyruvate carboxykinase
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio

SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
SRBC	sheep red blood cell
STEL	short-term exposure limit
STORET	Storage and Retrieval
T_3	triidothyronine
T_4	thyroxine
TdO	2,3-dioxygenase
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSH	thyroid-stimulating hormone
TRI	Toxics Release Inventory
TTR	transthyretin
TWA	time-weighted average
UDPGT	UDP-glucuronosyltransferase
U.S.	United States
UF	uncertainty factor
VLDL	very low density lipoprotein
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

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